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GENERALIZED HYPERTROPHIC OSTEOARTHROPATHY
A PATHOLOGIC STUDY OF SEVEN CASES *

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The association of digital clubbing with intrathoracic disease has been recognized since antiquity.[1] The wider distribution of the lesions of this malady with involvement of the shafts of the larger bones of the extremities has been appreciated only comparatively recently.[2,3] The syndrome which is termed generalized hypertrophic osteoarthropathy § may be defined as that condition occurring as a sequel of some major visceral disorder, usually intrathoracic in location, which is manifested by clubbing of the digits and ossifying periostitis, mainly of long bones, and is frequently associated with joint symptoms. Literature on the subject is not extensive and is for the most part concerned with the clinical findings, although the roentgenologic and gross pathologic features have been adequately described. During recent years Locke [4,5] and Mendlowitz [6] have recorded in detail the clinical aspects of the condition and Crump [7] has given an excellent analysis of the pathologic changes.

We have had the opportunity of examining the skeletal tissues from 7 cases of secondary hypertrophic osteoarthropathy in which all of the well known clinical and roentgenologic manifestations were represented. It is our purpose to present in detail the observed morphologic alterations in the bones and joints and to trace the sequences in the development of the major lesions of the syndrome.

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§ This nomenclature is preferred to the more frequently used term "pulmonary hypertrophic osteoarthropathy" in view of the occurrence of the condition in cases without evidence of pulmonary disease.

Material

The specimens serving as the basis for this study were obtained for biopsy or at necropsy from 7 men ranging in age from 18 to 65 years. Six of the patients had severe pulmonary disease and one suffered from congenital heart disease. Certain clinical pathologic data necessary for evaluation of the descriptive portions of the paper are presented briefly in Table I.

In order to facilitate presentation the observed changes have been described under four anatomical headings: *Periosteum, Cortex, Joints,* and *Clubbed Digits.* The description under each category is given as a composite of all the cases studied and is intended to portray, within the limits of the material available, the successive stages in the development of the peripheral lesions of generalized hypertrophic osteoarthropathy.

Pathologic Findings

Periosteum

In the early developmental stage of the osseous lesion the fibrous periosteum becomes thickened and exhibits signs of inflammation. Diffusely scattered lymphocytes in large numbers, less numerous plasma cells and, in some instances, polymorphonuclear leukocytes appear. Frequently the lymphocytes collect in dense aggregates in perivascular areas (Figs. 6 and 8). The adjacent extraperiosteal connective tissues are similarly affected but to a less marked degree. Coincidental with the appearance of the inflammatory reaction the periosteum becomes thickened and divided into two fairly distinct layers. The outer of these zones is more densely fibrous and it is here that the inflammatory cells accumulate in greater numbers. The inner cambial layer is comprised of one or several rows of swollen stellate or ovoid cells with vesicular nuclei and abundant amphophilic cytoplasm. Initially the fibrillary intercellular substance of this layer is loosely textured and edematous. This fibrillar material is soon replaced or obscured by the deposition of osteoid matrix. With this increment of new bone matrix, interposed between the original bone and the cambium (Fig. 5), the dual layered periosteum is displaced from the compact bone of the cortex.

Osteoid apparently is deposited first upon the dorsal or extensor surfaces of the affected bones and these predilective sites tend to exhibit a greater quantitative change throughout the disease. In the early phases the new bone exhibits no regular structure. Subsequently, however, as growth proceeds, the osteoid matrix assumes a palisade-like structure with poorly defined, homogeneous columns arranged perpen-

TABLE I

Clinical and Roentgenologic Data and Anatomical Sites of Material Studied

Case no.	Age	Underlying disease	Initial symptoms	Duration of underlying disease	Digital clubbing	Joint signs and symptoms			Bone tenderness	Roentgenologic examination		Material studied		
						Pain	Stiffness	Ankylosis		Clubbing	Long bones	Source	Bones studied	Joints studied
1	45	Pulmonary cancer	Pulmonary	3 yrs.	+	+	−	−	+	+	Marked periosteal lesion	Necropsy	Digits, tibia, fibula	Interphalangeal, ankle
2	38	Pulmonary cancer	Skeletal	2 yrs.	+	+	+	−	−	No films	Marked periosteal lesion	Necropsy	Tibia, femur	Knee
3	65	Pulmonary emphysema	Pulmonary	9+ yrs.	+	−	−	−	−	No films	No films	Necropsy	Digits	Interphalangeal
4	45	Pulmonary tumor	Skeletal	10 mos.	+	+	+	−	−	+	Marked periosteal lesion	Biopsy	Femur	Knee
5	52	Pulmonary cancer	Skeletal	Unknown	+	+	−	−	+	+	Marked periosteal lesion	Biopsy and necropsy	Digits, femur, tibia, fibula, patella	Interphalangeal, knee, ankle
6	18	Congenital heart disease	Cardiac	18 yrs.	+	+	+	−	−	+	No films	Necropsy	Digits	Interphalangeal
7	45	Pulmonary cancer	Skeletal	1½ yrs.	+	+	+	−	+	+	Marked periosteal lesion	Necropsy	Digits, metatarsals	Interphalangeal

dicularly to the bone surface (Figs. 7 and 8). With continued growth activity the periosteum displaces itself centrifugally, the columns are further elongated, and their deeper extremities become attenuated. They are then separated from each other by strands of edematous fibrous tissue not unlike that present in the cambial layer and probably representing prolongations of it (Fig. 8). This newly formed marrow tissue is highly vascular and contains a slight to moderate infiltration with lymphocytes. The trabecular narrowing is associated with active osteoclasis. In many regions, however, rows of osteoblasts remain and continue to add new layers of osteoid upon recently formed trabeculae (Figs. 6 and 8).

Shortly following its deposition the new subperiosteal bone layer becomes fused with the original cortical surface. Prominent cement lines persist, marking such points of union. The trabecular structure of the new bone also aids in distinguishing it from the pre-existing cortical compacta to which it is joined.

During periods of diminished periosteal activity mineralization progresses throughout the mass of osteoid and the palisaded columnar appearance is diminished or lost (Fig. 9). The peripherally situated new bone becomes more nearly continuous and, as a result of the union of many of the bony columns in this region, a pseudo-cortex is formed. This layer of condensed bone maintains its attachments to the true cortex by the persisting, radially arranged trabeculae. During such periods of relative inactivity the prominence of the cambial layer diminishes, the lymphocytic infiltration dwindles, and the periosteum returns to its resting stage (Fig. 11). The lesion may remain stationary at this stage or reactivation may occur.

Fluctuations in periosteal function probably are not wholly dependent upon activity of the basic disease in the thorax [6] but may be controlled in part by local factors since various phases of the skeletal lesions may be observed simultaneously in different bones in the same patient. There is considerable evidence of exacerbations and remissions in activity as attested by the appearance of the dual layered periosteum and the deposition of new columns of osteoid external to, but fused with, the thin pseudo-cortex described previously (Figs. 7 and 10). In this manner extracortical lamination is produced. As many as six such laminae have been described [8] although none of our cases exhibited more than two (Fig. 10).

As the result of centrifugal displacement of the periosteum the initially formed bone comes to lie at some distance from the cambium. In occasional specimens this distance was in excess of the thickness of the original cortex (4 to 6 mm.). Presumably as the result of physical stress

and variation in the vascular supply, and through the medium of osteoclastic activity, the original radial structure of the new bone is obliterated. The spongy textured bone replacing it soon acquires an arrangement similar to that of the normal cancellous bone of the medulla. The general alignment of the trabeculae is then parallel to that of the bony axis of the shaft (Figs. 11 and 12). The trabeculae gradually develop a normal internal lamellar structure.

The intervening marrow loses its fibrillar structure, becomes fatty, and occasionally evidence of focal hemopoietic activity is observed. Usually, however, there is no evidence of blood cell formation in the true medullary cavity at the same level. It is noteworthy that in the present study no constant abnormalities were found in the original marrow substance.

Coursing through the newly formed extracortical marrow are obliquely directed strands of fibrous tissue representing prolongations of fibers from the displaced periosteum. These penetrate to, and often into, the original cortical bone in the manner of Sharpey's fibers. They frequently encompass branches from the nutrient vessels in the original periosteum (Figs. 7 and 8). The subperiosteal bony trabeculae do not impinge upon or distort these fibrous strands. On the contrary it appears that the bone matrix is so deposited that it forms encasing tubular channels resembling Volkmann's canals.

At points of tendon insertion into the cortex an interesting variation of the periosteal disorder is encountered. Beginning at the tendo-osseous juncture and progressing into the tendons for distances up to 5.0 mm., there is progressive metamorphosis of tendinous tissue into fibrocartilage. The neighboring subperiosteal osteogenic lesion encroaches upon such areas and a replacement process simulating endochondral ossification may ensue (Fig. 13). The substitution of osteoid for fibrocartilage or hyaline cartilage is irregular and results in circumscribed but almost structureless masses of bone matrix. Ultimately, calcification occurs and the lesion assumes the appearance of an intratendinous osteophyte. A closely related change may appear in those ridges of bone to which membranous attachments occur (Fig. 14). This is particularly prominent in the linea aspera of the femur and the interosseous crests of the tibia and fibula.

The frequency and degree with which the various features of the periosteal lesion appeared in the present cases are shown in Table II.

Cortex

Following the deposition of subperiosteal bone and its fusion with the cortex as described in the preceding section, the configuration and

internal structure of the original diaphysis become modified. It has been indicated that the distinction between cortex and newly formed bone may be made during the greater part of the course of the disease. There is generally a slight difference in staining quality of the two parts and single or multiple cement lines persist at the points of fusion (Fig. 7). In long-standing lesions, however, these distinguishing fea-

TABLE II

Summation of Skeletal Changes

Case no.	Periosteum		Subperiosteal bone			Cortex			Joint lesions		
	Dual layers	Periostitis	Active bone formation	Lamination of new bone	Inactive new bone sheath	Cortical and periosteal layers fused	Osteoporosis of cortex	Bone proliferation in tendon	Synovitis	Degenerative changes in cartilage	Pannus
1	+	−	+	−	−	+	+	+	−	−	−
2	+	+	+	+	−	+	+	+	+	+	−
3	−	−	−	−	−	−	+	+	+	+	−
4	+	+	+	−	+	−	−	−	+	No cartilage studied	−
5	+	+	+	+	+	+	+	+	+	+	+
6	+	+	−	−	−	−	−	−	+	−	−
7	+	+	−	−	−	−	+	−	+	±	−

tures may become obscured (Figs. 10 and 11). In such instances it may be impossible to establish with certainty the limits of the original cortex. This is particularly true when, as the result of late changes, the structure of the latter has been modified (Fig. 12).

After the new periosteal bone is fully developed and calcified, numerous osteoclasts may be noted upon the now buried surface of the cortex and within the spaces of the haversian systems as well. Focal bone resorption produces bay-like surface irregularities which, after considerable enlargement, are filled with fatty marrow. Some of these become continuous with the enlarged marrow spaces in the subperiosteal bone sheath. Distinction between the original cortex and the layer of new bone is thus further obscured. Continuation of this resorptive trend results ultimately in similar cancellous structure in both periosteal and cortical bone. The shaft, therefore, is markedly thickened but spongy in character. Crump [7] and Janeway [3] observed concomitant resorptive activity upon the endosteal side of the cortex which they stated eventually caused an increase in the diameter of the

original marrow cavity. In the present cases, however, there was no evidence of either endosteal resorption or widening of the medullary space.

Joints

Six of the 7 patients complained of symptoms suggesting involvement of the articulations (Table I). The tissues removed from the interphalangeal joints of one subject (case 3), from whom no such symptoms were elicited, revealed chronic inflammatory changes in the synovia and well marked degenerative lesions in the articular cartilage (Table II). Of the 6 patients presenting clinical signs of arthritis, only one (case 1) failed to show pathologic changes in the articular tissues. Failure to demonstrate microscopic evidence of joint disease in this instance may have been due to the fact that only a portion of one astragalotibial joint and one interphalangeal articulation were removed for study.

In the 2 patients from whom the most representative specimens were removed (cases 2 and 5), pathologic examination revealed chronic synovitis and degenerative lesions in the articular cartilage surfaces (Figs. 16, 17, 19, 21, and 22). Pannus covering a portion of the patella was observed also in one of the knee joints (Fig. 20).

A specimen of synovia and articular capsule excised surgically from the knee of one patient (case 4) revealed, in addition to pronounced edema (Fig. 15), a moderate degree of chronic inflammation of the subsynovial tissues. Marked thickening of the walls of small and medium-sized blood vessels with occasional thrombosis was observed also (Fig. 18).

In case 6 the examination of articular structures was limited to the interphalangeal joints of one thumb. Slight diffuse lymphocytic infiltration in the synovial tissues and hyperemia were the only abnormalities observed.

From these observations it is apparent that the pathologic changes in the joints of patients with hypertrophic osteoarthropathy are varied in both severity and kind. It appears, however, that edema of the subsynovial tissue and the accompanying diffuse infiltration with lymphocytes and plasma cells comprise the most constant morphologic abnormalities. In the more markedly affected joints the infiltrating cells tend to accumulate in the perivascular areas of the subsynovial layer. These changes, which seem to occur concomitantly with the inflammatory reaction in the periosteal tissues adjacent to the articulations, sometimes are accompanied by moderate proliferative activity in the synovial membrane, leading to villous hypertrophy or, in rare instances, to the spread of pannus on the articular surface.

The same tendency to thickening of arterial walls through medial hypertrophy and subintimal proliferation that is frequently present in the periosteum may be found also in blood vessels of the articular capsule. The alterations observed in the surfaces of the articular cartilages are, for the most part, similar to those seen in degenerative joint disease.[10] Pallor of the cartilage matrix, accompanied in the more severely altered joints by fibrillation, often is evident. The free edge of the articular surface may be pitted, uneven, and the total thickness of the cartilage layer diminished. Focal resorption of subchondral bone trabeculae is observed frequently and a number of osteoclasts usually are present in these regions. Such resorption appears to be more marked in patients with generalized hypertrophic osteoarthropathy than would be expected with degenerative joint disease in those of comparable age. The extension of vascularized tufts of fibrous tissue into or through the calcified layer of subarticular cartilage noted in some specimens (Fig. 21) may lead to focal areas of resorption in the joint cartilage itself (Fig. 22). It is probable that these changes lead to an accelerated degenerative process in the superficial layer of the articular cartilage.

Clubbed Digits

All of the patients in the present series showed digital clubbing on physical examination. In the 5 patients from whom roentgenograms were available it was noted that the bulbous enlargement of the fingers and toes was due chiefly to alterations in the soft tissues. Roentgenograms of the hands of one patient (case 1) showed a few spur-like overgrowths of bone from the cortex of some of the terminal phalanges (Fig. 1). Specimens were obtained from the fingers and toes of 5 patients (Table I).

From the study of this material it is evident that the changes responsible for clubbing may be found exclusively or in large part in soft tissue layers. The collagen bundles in the corium appear swollen and there is widening of the interfascicular spaces. Enlargement of the rete pegs in association with narrowing of the epidermal papillae also may be present. Lymphocytic and plasma cell infiltration in the extra-osseous tissues, in a manner similar to that observed in the extraperiosteal connective tissues elsewhere, is present and may be more marked near the distal ends of the digits.

The walls of small and medium-sized arteries external to the periosteum frequently are thickened. This is due in great measure to hypertrophy of the medial layer, although subintimal thickening and

fibrosis also may be present. The caliber of the lumina of such vessels may be significantly diminished.

The periosteum of the terminal phalanges shows relatively little change when compared with other portions of the skeleton. The most constant change consists of a division of this layer into an outer fibrous and an inner cellular cambial zone. Slight or moderate lymphocytic infiltration may be present in the former. Sections of metacarpals or proximal phalanges of the digits showing minimal periosteal changes in the terminal phalanges may reveal well marked new subperiosteal bone formation.

Among the present specimens there was one in which several irregular deposits of osteoid matrix had occurred within the marrow cavity of a terminal phalanx. The cause of this unique lesion was not apparent. Another digit showed an incompletely calcified bony excrescence within a tendon at the site of its insertion into bone. This lesion was presumed to be representative of those giving rise to the spur-like bony overgrowths visible in the roentgenograms (Fig. 1). Microscopically, it was similar to the bony overgrowths occurring at tendon insertions in degenerative joint disease.[10]

Discussion

Marie [3] and Bamberger [2] first described the widely distributed osseous changes in the syndrome now known as generalized hypertrophic osteoarthropathy and established the process as a clinical entity. Digital clubbing, although long recognized, had not been related to generalized skeletal disease. It is quite universally agreed at the present time that enlargement of the acral parts, subperiosteal bony overgrowth, and joint lesions, when present, are all related manifestations of a single syndrome.[4-6,9,11,12]

In the majority of instances these peripheral changes follow a primary pulmonary disease which is either initially or secondarily of an inflammatory nature. Pulmonary tuberculosis, bronchiectasis, severe emphysema, primary or metastatic neoplasm of the lung or mediastinum, and suppurative lesions of the lung or pleura are the more common exciting conditions. Diseases of the heart, especially those of congenital origin and long-standing valvular lesions, also lead to the development of the syndrome. In addition, a number of extrathoracic conditions, notably pyelonephritis, dysentery, syphilis, alcoholism, chronic intoxication with phosphorus or arsenic, jaundice, and biliary cirrhosis have been held responsible.[4,13]

The syndrome is known to be more common before middle life and

to affect males much more frequently than females. A congenital form of digital clubbing also has been recognized but this condition differs from the secondary syndrome in that there are no associated changes in the long bones, and related joint symptoms are absent. A further dissimilarity has been indicated by the studies of Mendlowitz [14] who found evidence of increased blood flow in the finger-tips in patients with all types of clubbing except the hereditary form.

The local factors concerned with the development of hypertrophic osteoarthropathy remain obscure although numerous hypotheses have been ventured. Bamberger [2] attributed the condition to a circulating toxin derived from the underlying suppurative disease, but considered the possibility that the osseous changes might result also from the therapeutic use of such chemical agents as phosphorus or arsenic. Marie [3] believed that irritative toxins elaborated by the decomposition of static secretions in bronchiectatic cavities were responsible. More recent observers, impressed by the great frequency with which osteoarthropathy is associated with pulmonary tuberculosis or other chronic pulmonary infections, have adopted the "toxic" theses of Marie and Bamberger. Mauer [15] has introduced the interesting concept of alteration in red cell suspension stability which, despite accelerated acral blood flow, leads to peripheral arterial anoxia. The presence of increased peripheral vascular flow is attested by the studies of Charr and Swenson [16] and by Mendlowitz.[14]

The occurrence of the syndrome in patients with congenital heart disease in whom no infectious lesions are demonstrable has led other observers to the belief that imperfect blood oxygenation resulting from either defective intrapulmonary aeration or impedition of vascular outflow from the lungs is the responsible disturbance. It has been suggested also that interference with circulatory function, due either to pulmonary or to cardiac lesions, may act in combination with toxins produced by associated infectious processes to produce the syndrome.[11,17] Because of the symmetric distribution of the skeletal changes, the possibility of neurogenic factors also has been considered.[5,18] In several instances the process has been thought to be the result of disordered endocrine function.[19]

It is clearly evident that these theories have given no precise explanation for the mechanism underlying the varied skeletal and soft tissue lesions of the syndrome. It appears probable that real progress toward the solution of the problem of etiology must await the development of an improved method whereby the lesions can be produced experimentally. Since the disease is reported as a relatively frequent spontaneous

occurrence in the dog,[20] an experimental method would seem to be available.[21]

The physical signs and the symptoms leading to the clinical recognition of hypertrophic osteoarthropathy are extremely varied.[5,17,22] In the majority of cases widening of the terminal portions of the fingers and toes, with or without excessive curvature of the nails, is the first abnormality noted. Many patients, however, complain of intermittent pain and tenderness along the extremities. Stiffness and tenderness elicited by movement of the peripheral joints frequently are noted.[5,8,12,22,23] Occasionally advanced periosteal lesions may be visible in the roentgenogram before the condition is suspected by either patient or physician. Not uncommonly, signs and symptoms pointing to the presence of the skeletal changes may antedate those referable to the primary visceral disease.[24]

The anatomical findings aid one in explaining the varied clinical manifestations. The enlargement of the fingers and toes is due to an increase in the bulk of the soft tissues around the terminal phalanges and beneath the nails. Although some uncertainty prevails concerning the exact nature of this soft tissue change and its relationship to the ossifying process elsewhere in the skeleton, it is apparent that hyperemia, edema, increased amounts of loosely textured connective tissue, and mild chronic inflammation are the predominant features of the lesion.[5,12,22,25-28] All tissue layers from the epidermis inward to the periosteum may be affected in varying degree, the most marked change occurring in the terminal portions of the digits. It is not surprising, therefore, that clubbing may develop within relatively short periods of time or regress promptly during remissions of the underlying visceral disease.[6,24] Bony overgrowth leading to "spurring" or "mushrooming" of the terminal phalanges occasionally develops in the more severely affected patients. Such osseous lesions develop in previously enlarged digits and thus contribute little to the acral deformity. In children the amount of soft tissue swelling may be such that the terminal phalanx may undergo pressure atrophy.[29]

The osseous lesion begins as a low-grade inflammatory reaction in the periosteum. This is followed by a remarkable degree of subperiosteal new bone formation with centrifugal displacement of the thickened periosteum. These changes may occur fairly rapidly and may thus induce pain and tenderness. Slowly progressive or quiescent lesions tend to be asymptomatic.

The periosteal changes usually are observed first along the distal third of the bones of the forearm and leg. Progression, although very

irregular, is usually toward the proximal portions of these bones. At a later stage similar lesions appear along the lower ends of the femur and humerus (Fig. 4). Still later there may be involvement of the shafts of the metacarpals and metatarsals and less frequently of the proximal and middle phalanges. The changes usually are bilaterally symmetric. There is a tendency for the process to be more marked on the dorsal and medial surfaces although pronounced lesions are especially likely to develop in areas where tendons insert.[7,8,30] The productive changes beneath the periosteum diminish near the expanded ends of the diaphyses and rarely are present in areas covered by articular capsules (Figs. 2 and 3). Although microscopic alterations are frequent in the terminal phalanges and in the tarsal and carpal bones, lesions distinguishable by clinical or roentgenographic examination rarely are observed in these areas.[5,12,22,31] In addition to the predilective sites of bony overgrowth noted in the present study, lesions have been described by others in the clavicle, scapula, patella, and iliac crests, and enlargements of the nose and malar prominences have been recorded.[22,27,28,31,32]

It has been noted in the present study that certain portions of the skeleton may show rapidly progressing periosteal lesions while in other areas in the same patient the process is stationary or undergoing resolution. These differences in activity afford an explanation for some of the observed variations in symptoms and also suggest that certain purely local factors must play a part.

Although the pathologic changes in articular structures often are slight in comparison with those in the neighboring periosteum, there are certain similarities in the reactions. Edema and mild chronic inflammation of the synovia and inner portions of the articular capsules are the most constant changes in painful joints. These have their counterparts, varying only in degree, in the periosteal process. The character of the synovitis, however, differs in no significant manner from that noted in other forms of painful articular disease. It appears probable, therefore, that the symptoms of joint pain and stiffness are caused chiefly by the arthritis associated with secondary osteoarthropathy and are not necessarily to be attributed, as some observers have suggested,[30] solely to the adjacent periostitis. There is little doubt, however, that the periosteal changes frequently are responsible for some of the symptoms which are considered both subjectively and objectively to have origin in the joint.

Proliferative and inflammatory changes in the synovial tissues of a degree sufficient to cause ankylosis are observed rarely. However, as shown in our case 5, pannus may develop occasionally and lead to ad-

hesions across the joint space. The actual relationship of the degenerative changes in the articular cartilage to hypertrophic osteoarthropathy is not altogether clear in the present study. The only microscopic difference between such degenerative lesions in our patients and in otherwise healthy persons of comparable age is the presence of resorptive changes in the subchondral bone and the penetration of vascularized tufts of marrow tissue into or through the calcified layer of cartilage. It is possible that this may be nothing more than a result of atrophy of disuse.

Summary and Conclusions

A pathogenetic pattern has been developed on the basis of a detailed study of the skeletal lesions of generalized hypertrophic osteoarthropathy as observed in 7 cases.

The most striking finding consisted of a productive periostitis involving the long bones of the extremities. In this location the process showed variously an inflammatory periostitis characterized by lymphocytic and plasma cell infiltration, subperiosteal new bone formation, and the production of a pseudo-cortex which ultimately fused and expanded the original cortex. There was evidence to suggest intermittent activity of the periosteal lesion.

During the course of fusion of the original cortex and the newly formed subperiosteal bony sheath, the former exhibited resorption and adaptation to increased shaft diameter.

Articulations in involved extremities were the seat of mild to moderately severe chronic synovitis associated with non-specific degenerative changes in the articular cartilages.

Clubbing of the digits appeared to result from an increase of soft tissue bulk and was associated with few or no morphologic changes in the terminal phalanges.

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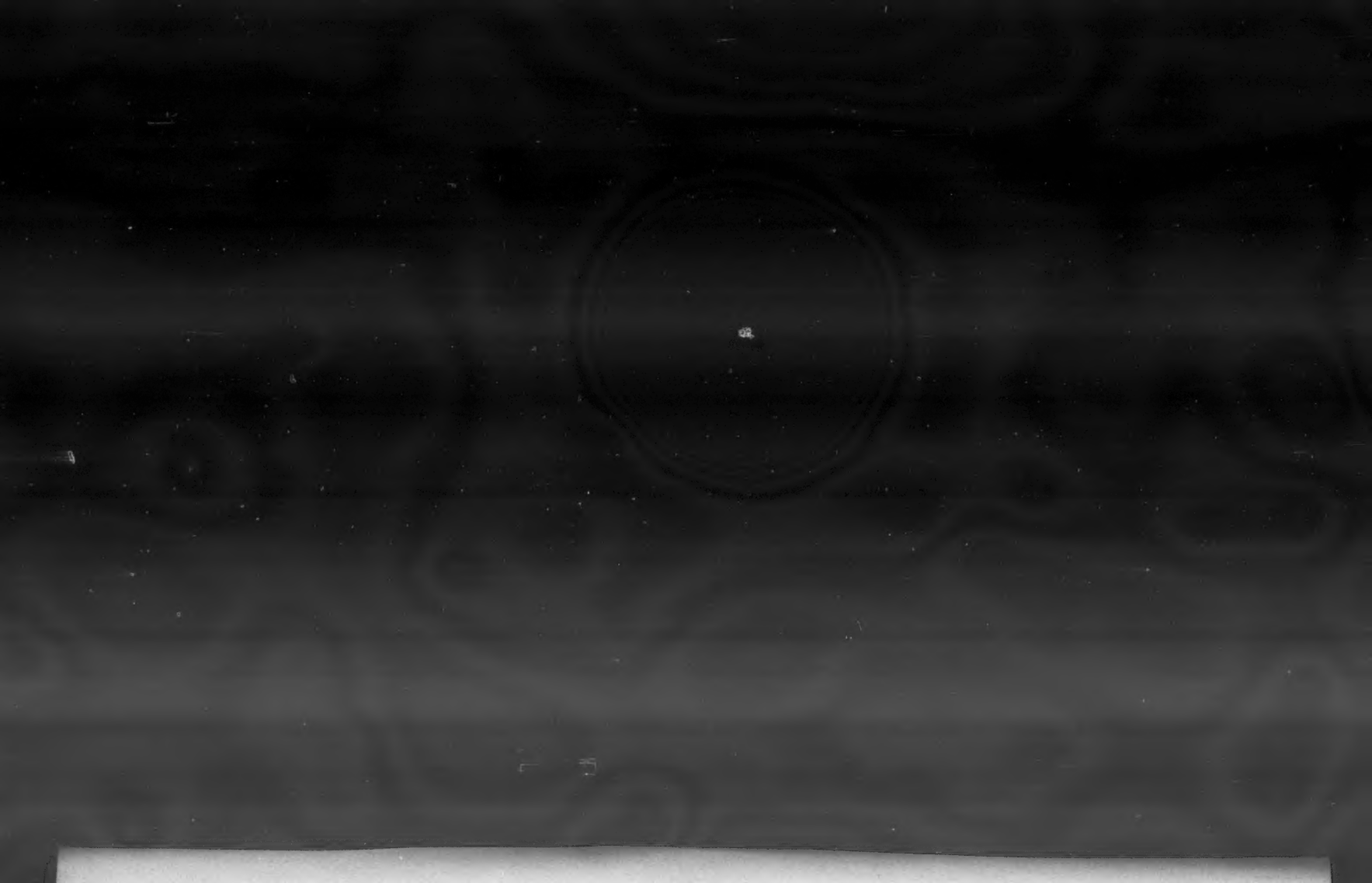
[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 61

FIG. 1. A roentgenogram of the hands in case 1. Expansion of the soft parts of the finger-tips is evident and there is pronounced spurring of the terminal phalanges. Save for isolated points, presumably of tendon insertion, there is no detectable periosteal reaction.

FIG. 2. A roentgenogram of the ankles in case 5. The periosteum of the tibia and fibula is thickened and calcified. The process is more marked over the medial aspect of the bones.



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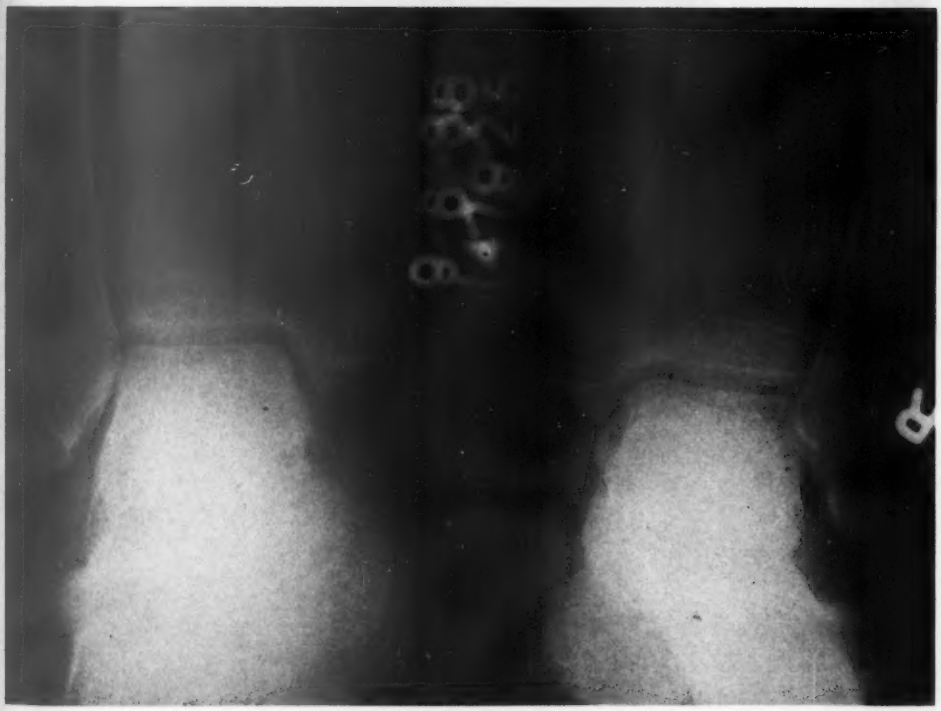

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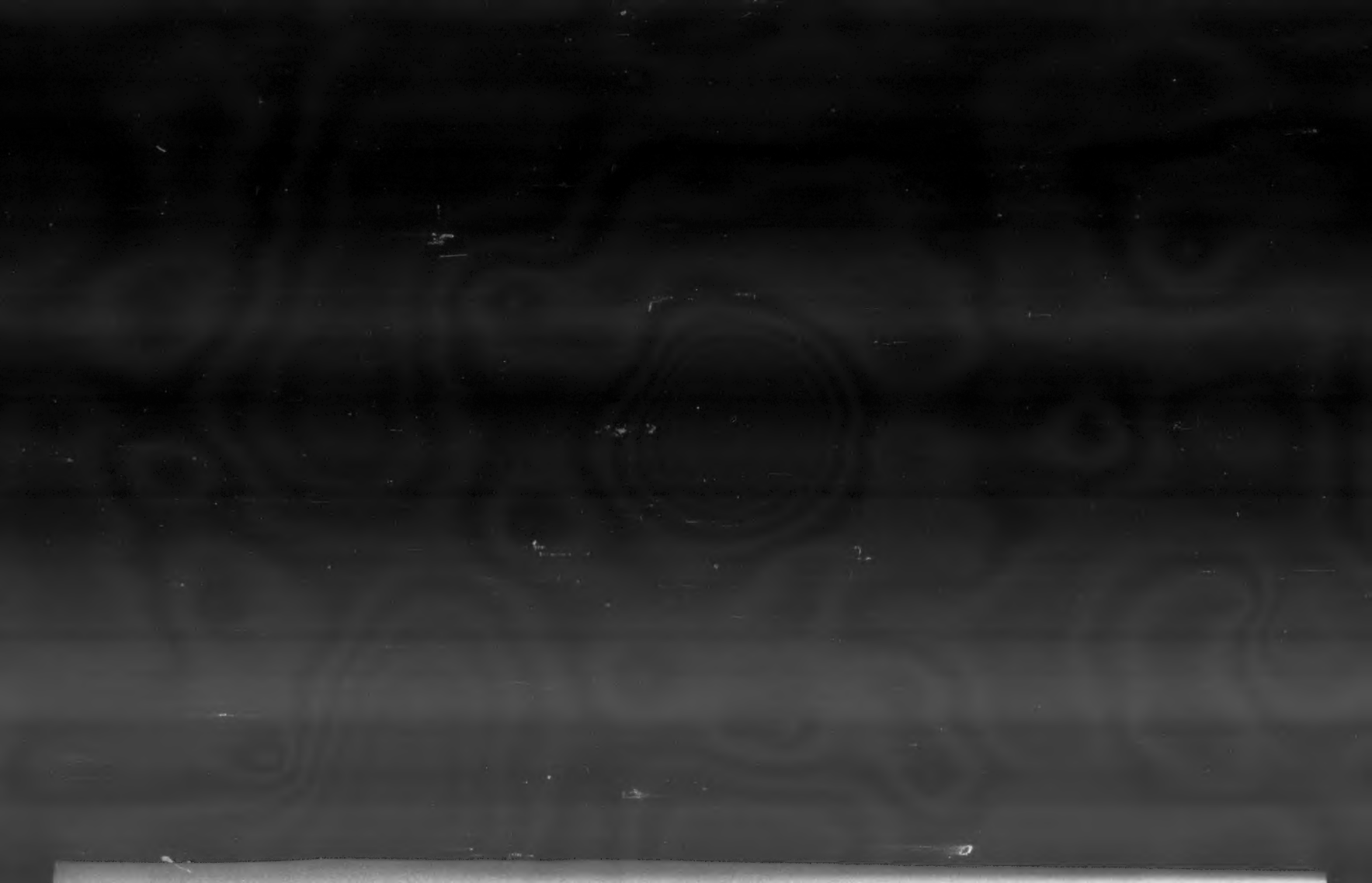
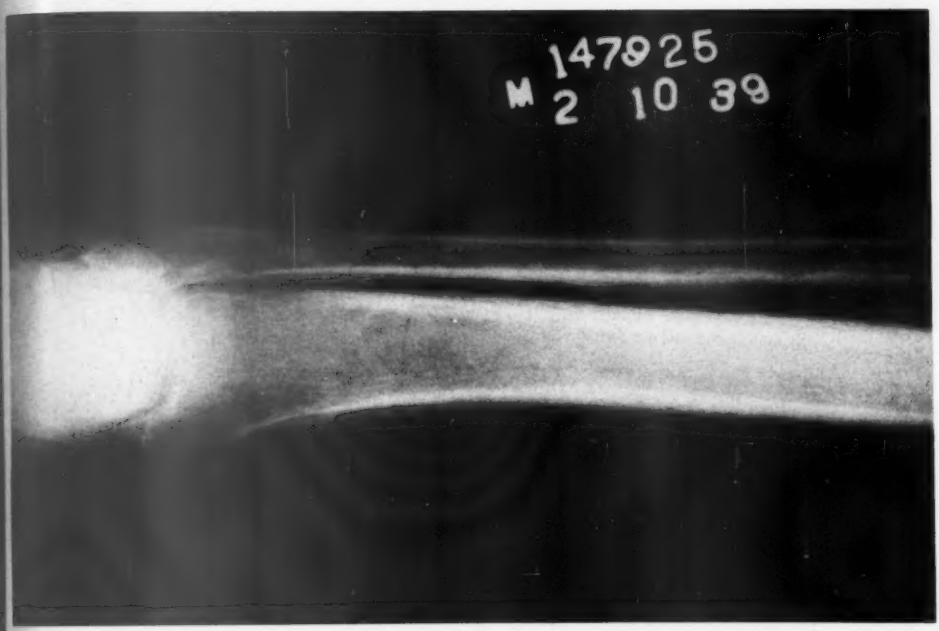
PLATE 62

FIG. 3. A roentgenogram of the left leg in case 5, taken 5 months after that shown in Figure 2. The periosteal lesion extends well up the shafts of the tibia and fibula and is now thicker and more mottled than previously. The predilection for the medial sides of the bones again is apparent.

FIG. 4. A roentgenogram of a knee in case 5. The joint and upper portions of the tibia and fibula reveal only minimal changes. A marked subperiosteal overgrowth of bone upon the femoral shaft is apparent.





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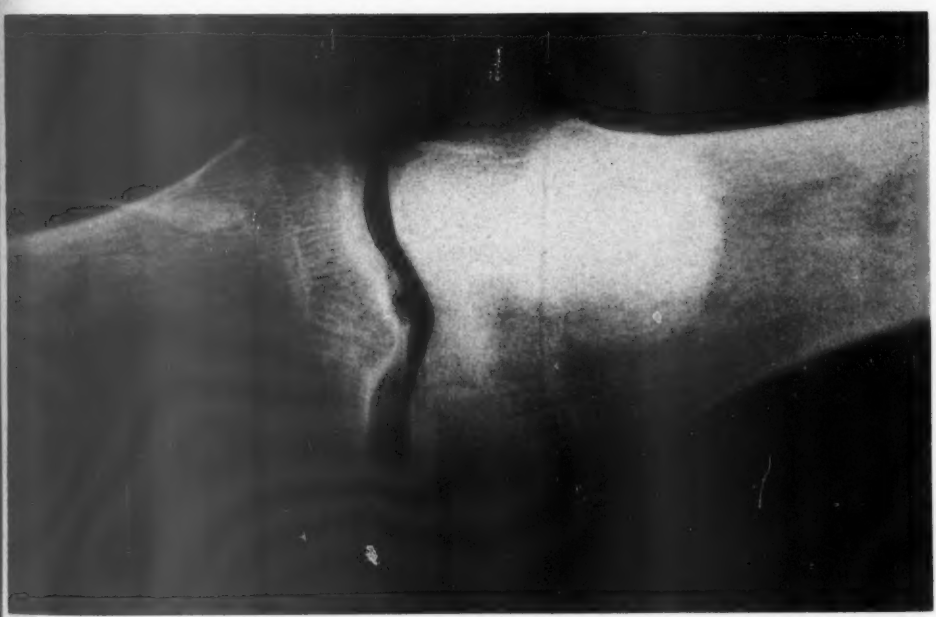

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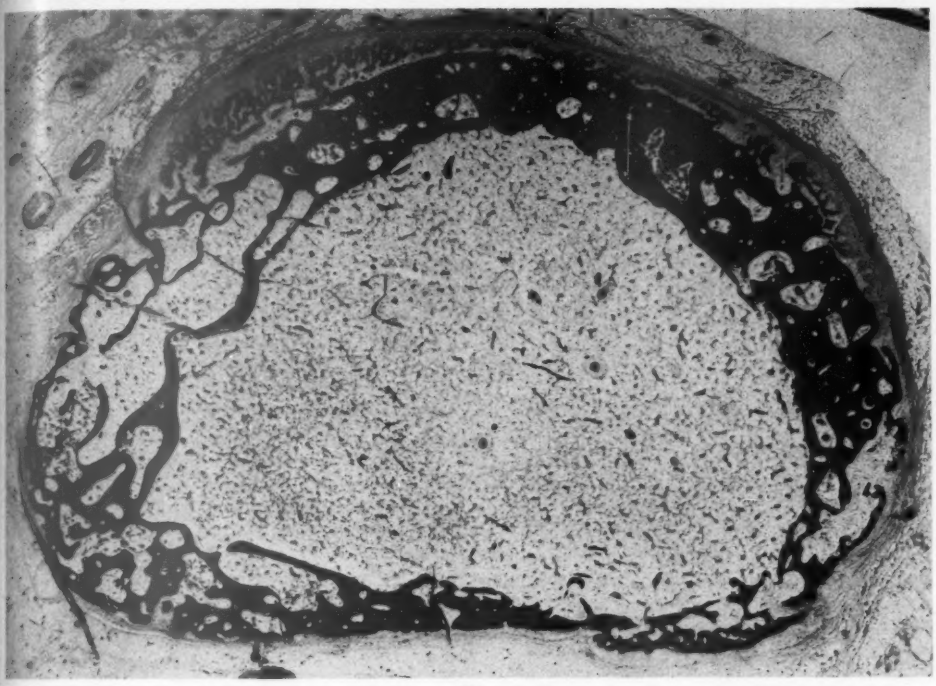
PLATE 63

FIG. 5. A cross section through a metatarsal in case 5. The periosteum on the dorsal and medial aspects is thickened and divided into an outer fibrous and an inner cambial layer. There is an irregular deposit of new bone upon the cortex. The latter shows considerable osteoporosis. × 11.

FIG. 6. Specimen taken for biopsy from the periosteal surface of the lower end of the femur in case 5. The fibrous periosteum is dual layered and the outer coat contains an inflammatory reaction. Subperiosteal trabeculae are still arranged perpendicularly to the periosteum. Short rows of osteoblasts affixed to the trabeculae have caused a deposit of thin osteoid seams. Marrow tissue within the newly formed bone is edematous, fibrillar, and vascular. × 56.



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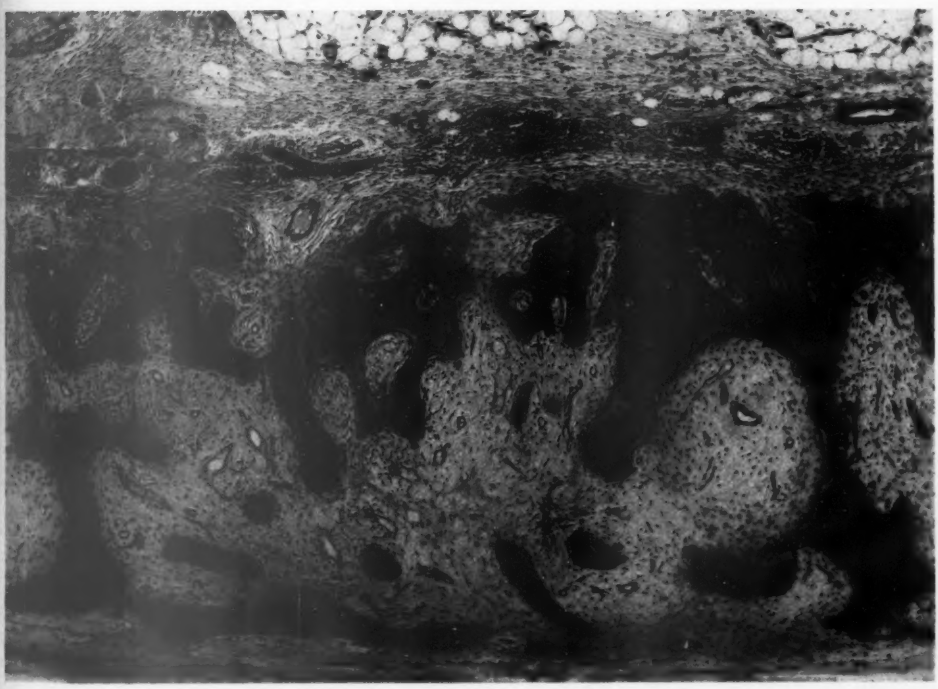

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PLATE 64

FIG. 7. A cross section through the wall of the femur in case 5. The columns of new bone are arranged in palisade fashion. Ossification is more advanced in the deeper portions. The point of fusion with the cortex is manifested by a densely staining but broken cement line. Blood vessels entering from the periosteal layer are perpendicularly placed and form a series of arcades. × 11.

FIG. 8. A higher power view from the same section as that used for Figure 7. The periosteum is dual layered and contains a marked round cell infiltration within its outer zone. The columns of osteoid are calcified in their deeper reaches. The tissue intervening between the trabeculae is fibrocellular. One of the penetrating blood vessels is apparent. × 56.

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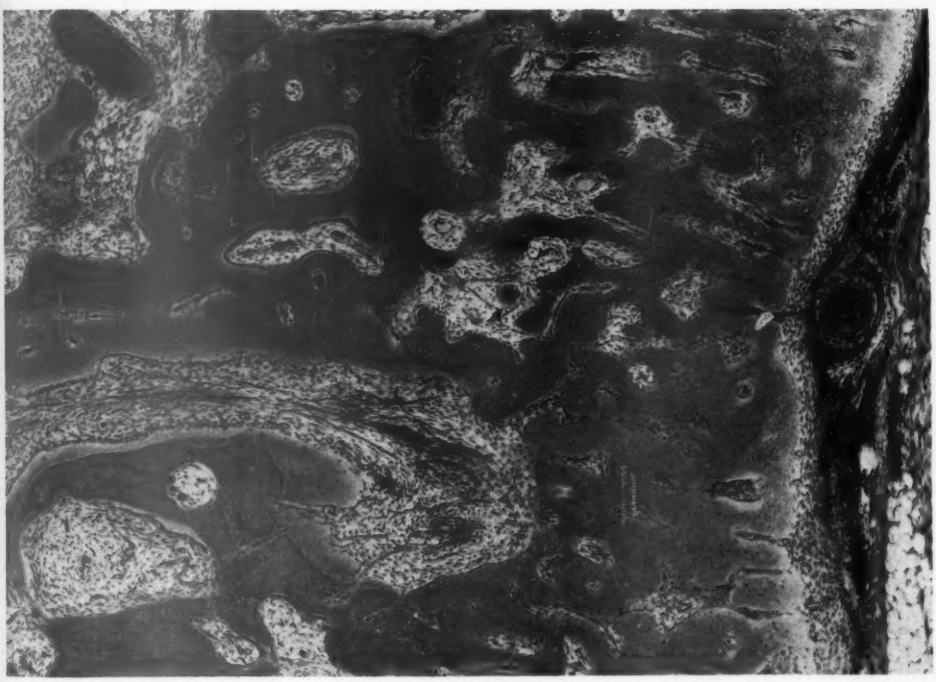


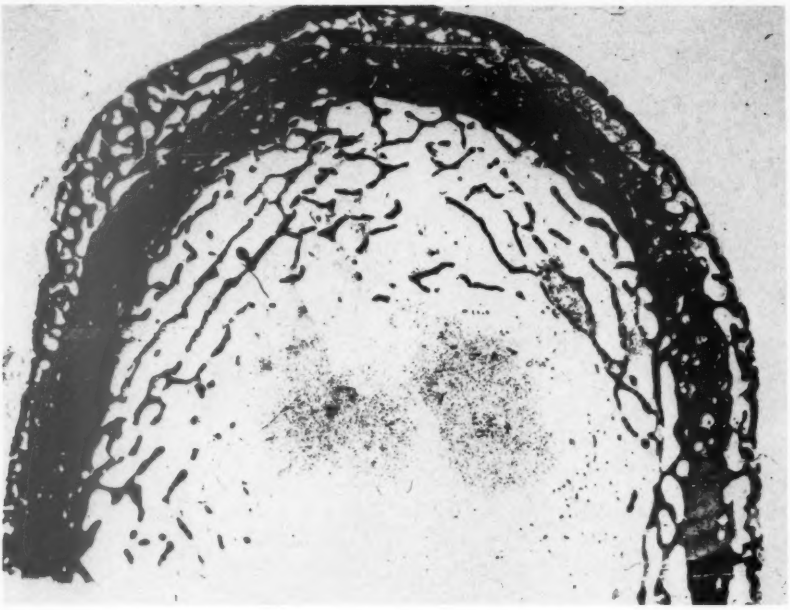
8

Gall, Bennett, and Bauer Generalized Hypertrophic Osteoarthropathy

PLATE 65

FIG. 9. A cross section of the tibia in case 2. There is no evidence of osteogenic activity at this time. The bone previously deposited has formed a cancellous sheath about the old cortex which now shows foci of lacunar resorption. The radial appearance of the trabeculae has disappeared and a well defined pseudo-cortex has been formed. × 2.

FIG. 10. A cross section of the fibula in case 5. Apparent transient arrest in activity with completed mineralization has permitted ensheathment of the shaft by a thick layer of cancellous bone. Early lacunar resorption in the original cortex has begun to obscure distinction between the two layers. Evident reactivation of the process has produced a new layer of osteoid superimposed upon the pseudo-cortex with resultant lamination. × 13.



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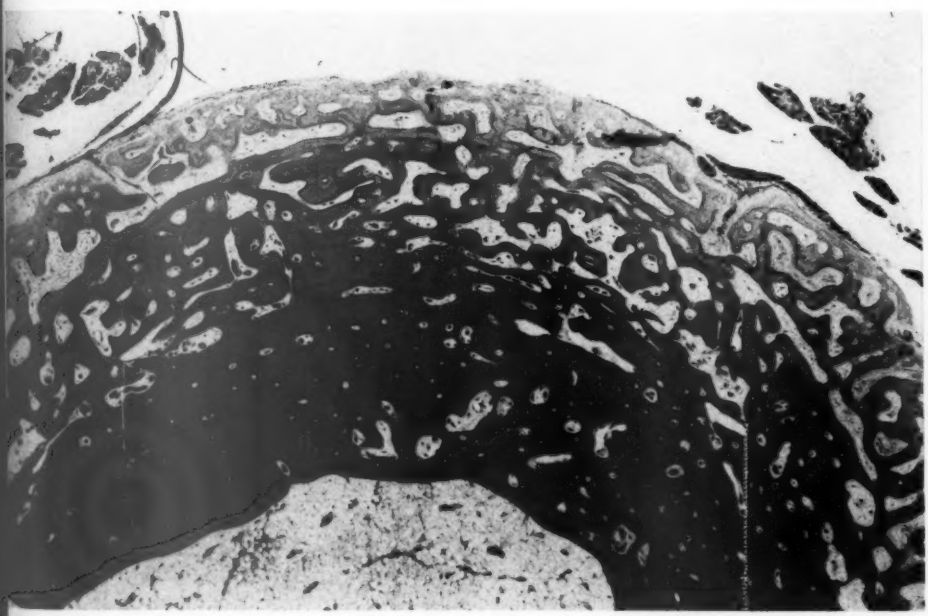

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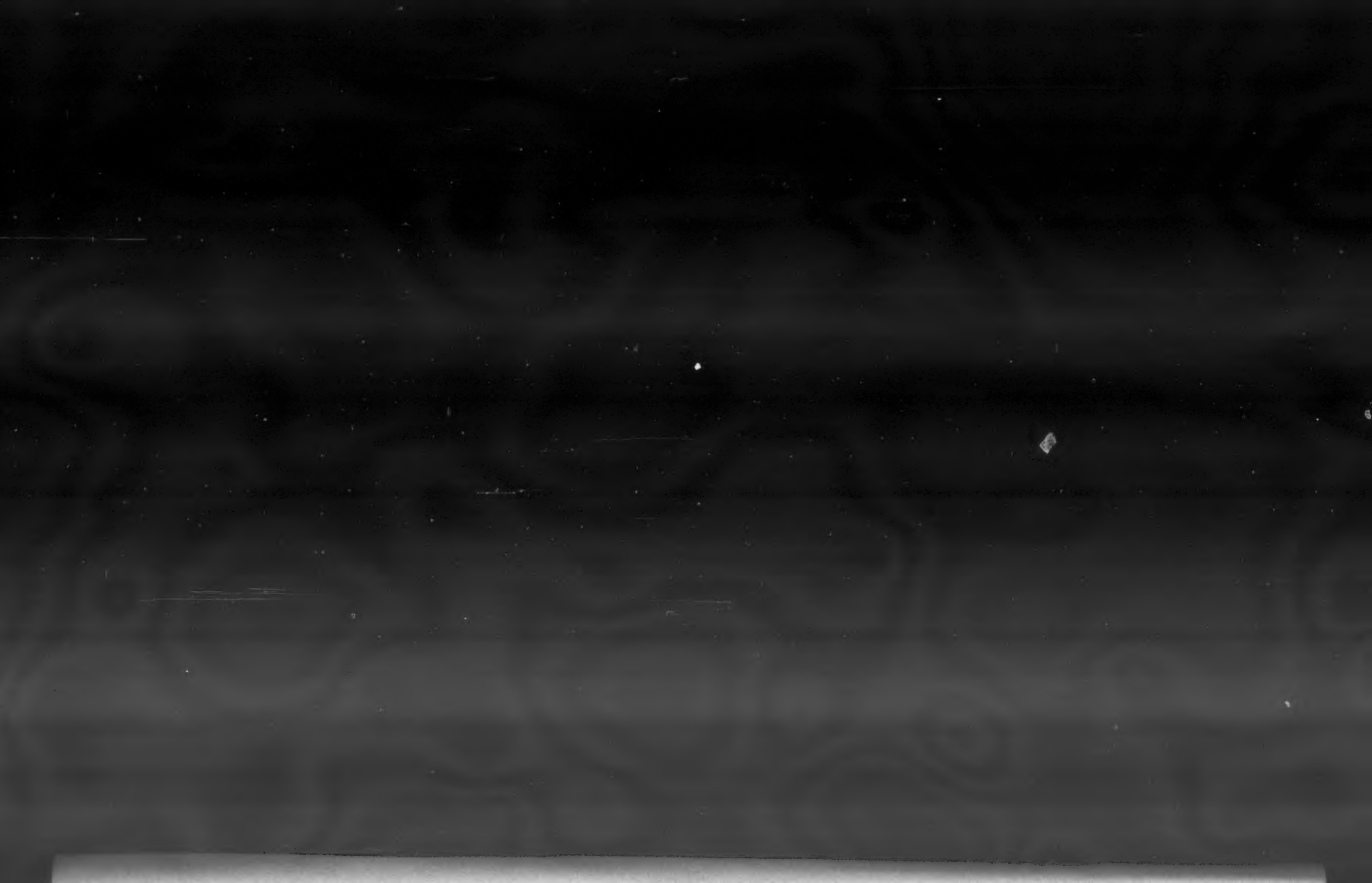
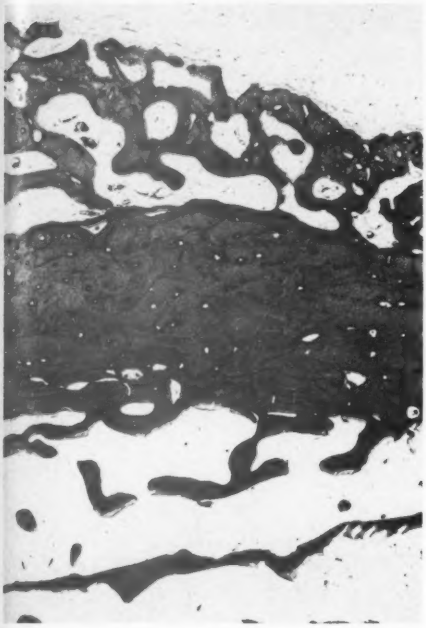
PLATE 66

FIG. 11. A higher power view of the section shown in Figure 9. Fusion of the cancellous sheath and old cortex as well as the formation of a pseudo-cortex is apparent. × 13.

FIG. 12. A longitudinal section from the tibia in case 1. Lacunar resorption of the outer portion of the true cortex has caused it to become as cancellous as the subperiosteal sheath. It is difficult to distinguish between the newly formed and the original cortical bone. There is no evidence of resorption from the endosteal side. × 13.

FIG. 13. A tendon attachment on the femur of case 2. Irregular masses of osteoid have extended into the substance of the tendon. × 54.





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Gall, Bennett, and Bauer Generalized Hypertrophic Osteoarthropathy

PLATE 67

FIG. 14. A higher power view of one prong of the linea aspera in the lower one-third of the femur of case 5. An exaggerated deposit of osteoid has produced an osteophyte-like structure which is here closely related to the adjacent sheath of periosteal new bone and not to the underlying true cortex. × 13.

FIG. 15. A section of synovial membrane from the knee in case 4. The surface layer is intact but there is considerable edema of the subsynovial tissues. × 110.

FIG. 16. A section of synovial tissue from the knee in case 2. There is edema in the subsynovial layers and lymphocytic infiltration superficially. × 110.

14

15

16

Gall, Bennett, and Bauer

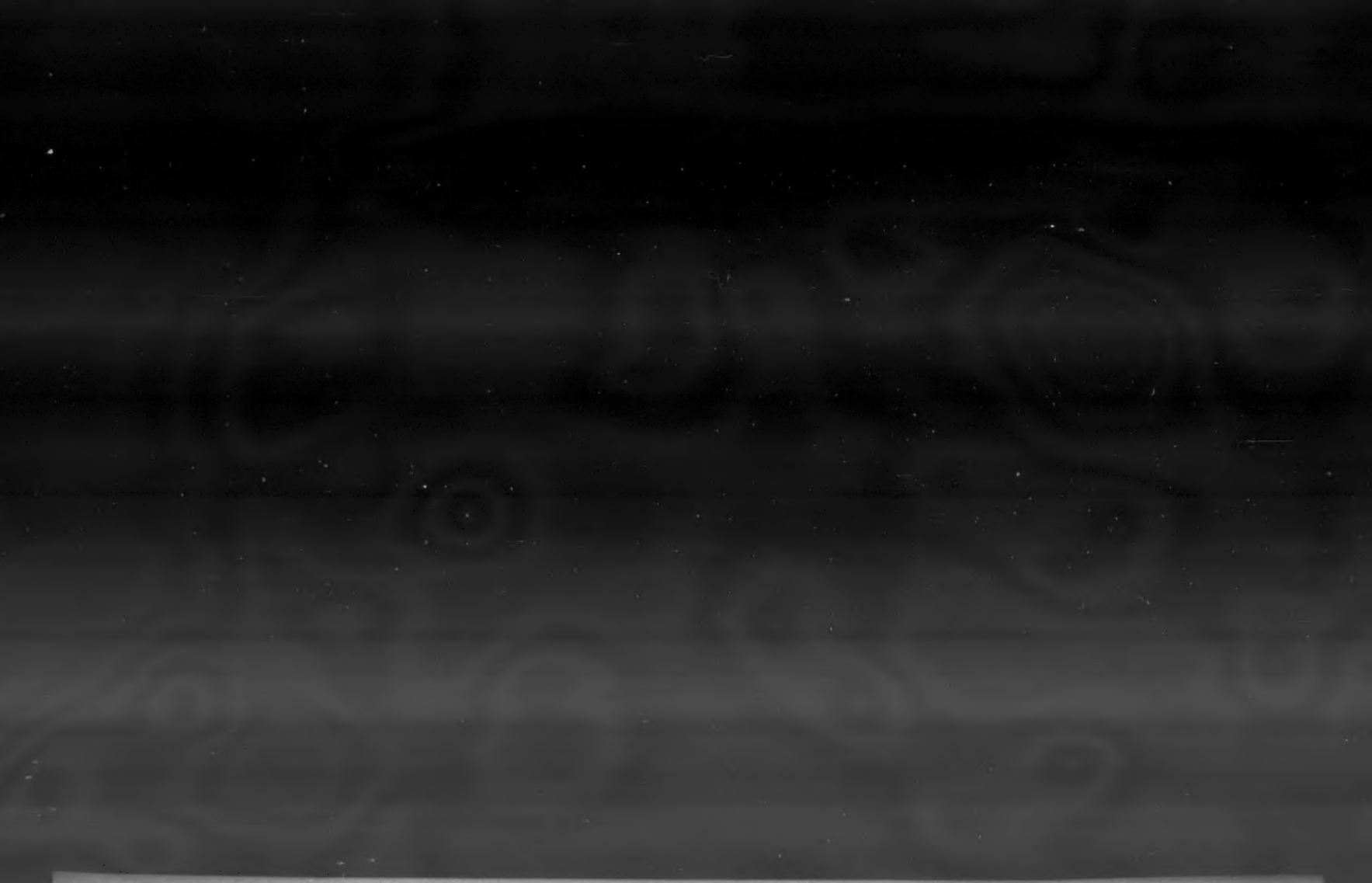
Generalized Hypertrophic Osteoarthropathy

PLATE 68

FIG. 17. A section of synovia from the knee in case 5. Edema and lymphocytic infiltration of the subsynovial tissue are apparent. × 106.

FIG. 18. A section of subsynovial tissue from the knee in case 4. There is scarring with marked fibrous mural thickening of arteries. Arterial lumina are markedly narrowed. × 106.

FIG. 19. A section from the margin of the articular surface of a femoral condyle in case 5. Nests of loose fibrillar tissue and focal areas of bone resorption are present in the subchondral trabeculae and calcified cartilage. × 54.



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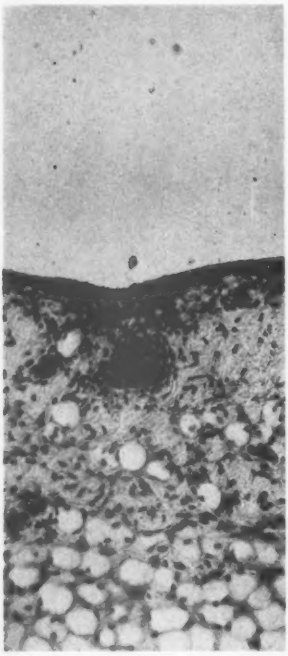

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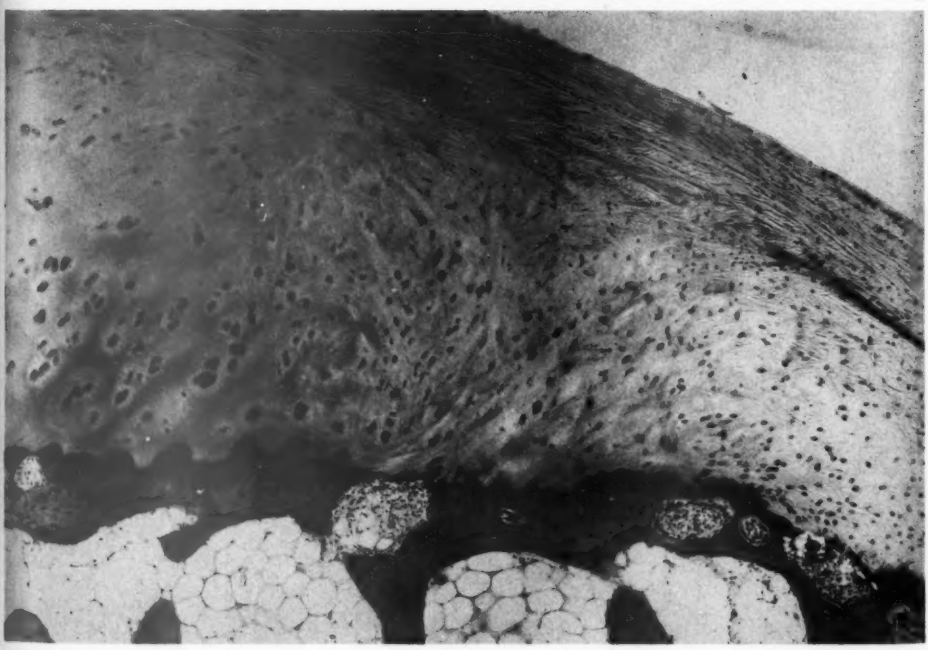

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PLATE 69

FIG. 20. A section showing a defect in the patella of case 5. The surface of the cartilage is irregular, eroded, and affixed to it is a thin strand of pannus. × 12.

FIG. 21. Another section from the specimen shown in Figure 20. A large area of cartilage resorption is shown. × 97.

FIG. 22. A section of subchondral plate from the femoral condyle in case 2. A tongue of vascular connective tissue infiltrated with lymphocytes has perforated the bone and is eroding the overlying cartilage matrix. In the latter, lacunar aggregations of degenerated cartilage cells are apparent. × 97.

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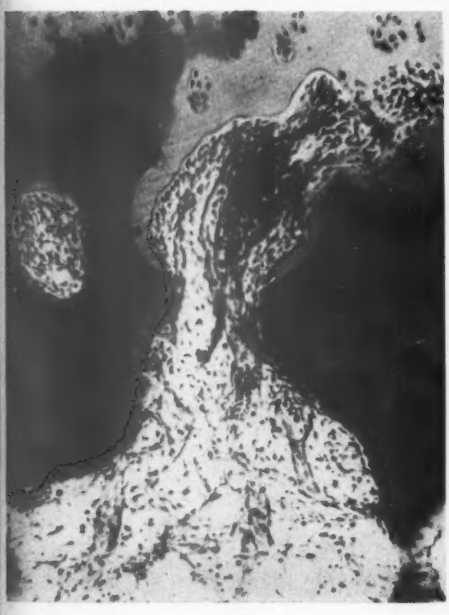

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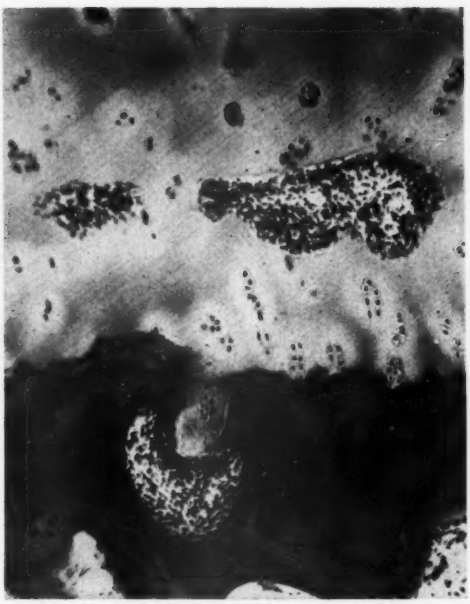

22

Gall, Bennett, and Bauer Generalized Hypertrophic Osteoarthropathy

METASTASIZING CARCINOMA OF THE PARATHYROID GLAND WITH OSTEITIS FIBROSA CYSTICA AND EXTENSIVE CALCINOSIS*

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The case described in this paper provides one of the few examples of metastasizing carcinoma of the parathyroid gland studied post mortem, and it has unusual interest because of the functional derangements produced by the tumor. Intensive clinical and laboratory studies were made over a prolonged period, and post-mortem examination was complete.

CLINICAL OBSERVATIONS

The patient was a white housewife, 29 years old, who entered the New York Hospital on June 29, 1949, because of the recurrent symptoms of hyperparathyroidism. In 1943, during her first pregnancy, she had developed extreme fatigue, nausea, and vomiting which persisted until the delivery at term of a malformed baby who died at the age of 5 weeks of congenital heart disease. Her health did not improve after delivery. Nausea and vomiting ceased. Her appetite was seriously impaired; fatigue and weakness persisted. Severe pains developed about many joints and in the back. Over a period of 1 year she lost 40 lbs. in weight. In November, 1944, a specimen was taken for biopsy from a cystic lesion in the right mandible and was diagnosed as giant cell tumor and osteitis fibrosa. In July, 1945, roentgenograms revealed numerous cystic lesions involving the ribs and long bones. The level of the blood calcium at this time was 20 mg. per cent; the phosphorus, 4 mg. per cent. Surgical exploration revealed two tumors which were regarded pathologically as adenomas of the parathyroid gland. The operation was followed by apparent restoration of health. The lost weight was regained and strength returned. Five months later the cystic lesions were reported as completely restored on roentgenologic examination and the serum calcium level was normal.

For 2½ years, and even during the course of a completed second pregnancy, she remained entirely well until in March, 1948, with the beginning of a third pregnancy, she experienced nausea, vomiting, weakness, and pain and aching over the right hip and iliac crest. Pregnancy was interrupted at the sixth month by a cesarean section and the fallopian tubes were tied. Her symptoms, however, did not abate following delivery and in March, 1949, roentgenograms revealed recurrence of the cystic lesions. The kidneys showed rather extensive diffuse parenchymal calcification. The serum calcium level was 22 mg. per cent. Her neck again was explored, with the removal of three parathyroid tumors measuring 2 by 1.5 by 1.5, 1.5 by 1 by 0.5, and 1.2 by 1 by 0.5 cm. Postoperatively her symptoms continued. She vomited at frequent intervals, thirst became extreme, constipation was obstinate, and her weakness was profound. After 3 months she entered the New York Hospital. Examination revealed considerable emaciation. Her legs were bowed and she walked with a limp. The thyroid gland was palpable, but no nodules could be detected in the region of the previous operations. Her muscles were extremely lax. Tender points could be demonstrated at various places over the bones of the forearm, the iliac crests, thighs, and legs.

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Received for publication, July 28, 1950.

The urine was of low specific gravity with numerous leukocytes and with cultures positive for *Escherichia coli*. Phenolsulfonphthalein excretion was only 10 per cent in 2 hours. Intravenous pyelograms exhibited diminished renal function. The Sulkowitch test for calcium was 4 plus. The blood urea nitrogen was elevated only moderately at 22 mg. per cent. The level of the serum calcium varied between 14.5 and 18.7 mg. per cent. Phosphorus values varied between 3.5 and 4.6 mg. per cent. Alkaline phosphatase was 15.7 units. Roentgenologic examination showed nephrocalcinosis, numerous areas of osteitis fibrosa cystica, and two small, nodular densities in the left lung field. The series of x-ray films taken at the time of admission failed to reveal calcification of vessels except for one small segment of the left axillary artery.

On a diet containing 130 mg. of calcium and 670 mg. of phosphorus over a period of 6 days the urinary excretion varied from 565 to 995 mg. of calcium and 808 to 921 mg. of phosphorus. Increase in calcium intake to 680 mg. and later to 2.026 gm. did not materially increase the excretion of calcium in the urine. On July 14, 1949, at a third operation, the left lobe of the thyroid gland was removed. Within it there were two small, nodular, white, firm, encapsulated masses which were diagnosed microscopically as carcinoma, since metastatic lesions were present in the left lung. Postoperatively the level of blood calcium remained unchanged and that of the urinary calcium was elevated. On July 25, 1949, two metastatic nodules with diameters of 0.9 and 1.2 cm. were removed from the upper and lower lobes of the left lung. Severe bone pain, nausea, vomiting, and anemia continued, together with elevated levels of blood and urinary calcium. Cough became an increasingly troublesome symptom and roentgenograms of the lungs taken during the course of her illness showed constantly expanding opacities which were interpreted clinically as probable carcinomatous extensions (Fig. 1).

On October 4, 1949, estrogen and testosterone therapy was instituted. This was done with the hope that these agents might act to remineralize the skeleton and thereby diminish the bone pain. Testosterone was given in doses of 25 mg. and progynon in doses of 10,000 rat units daily from October 4 to November 21. Calcium values for the week preceding this treatment ranged from 15.8 to 17.0 mg. per cent. Four days after treatment was started, the value was 12.8 mg. per cent, and for the remainder of the course varied between 11.8 and 13.9 mg. per cent. For a short period, pains were less marked and weakness seemed to be less profound. Racking cough, however, caused great distress. On November 17 it was noted that both hands were becoming pallid and cyanotic. Pulsation could not be observed in the radial or ulnar arteries. Roentgenograms revealed extraordinary calcification, not only of these vessels, but of almost all vessels of the extremities. Death occurred on November 24, 1949, approximately 6 years after the onset of symptoms.

Findings at Necropsy

The body was that of a well developed but poorly nourished white female. There were well healed surgical scars over the thyroid area and the left 6th rib. All of the teeth were absent except for the right lower premolars. There were superficial ulcers over both knees, 2 cm. in diameter.

The left lobe of the thyroid gland was absent. The right lobe was normal and on the posterior aspect three parathyroid glands measuring 3 to 6 mm. were identified. The cervical and supraclavicular lymph nodes were enlarged, gray, and soft.

The heart weighed 250 gm. The valves were normal except for extensive calcification of the annulus fibrosus of the mitral ring. The right and left coronary arteries were widely patent and only slightly calcified. A small artery within the interventricular septum was extensively calcified as shown by roentgenologic examination. The tips of the papillary muscles in the left ventricle at the insertion of the chordae tendineae were calcified.

The aorta was elastic and showed little atherosclerosis. However, all of its major branches were extensively calcified to their terminal divisions, as revealed by both gross anatomical and roentgenologic examinations (Fig. 2). Several small branches of the pancreaticoduodenal artery were occluded by calcific deposits. Branches of the splenic artery likewise were completely occluded by a calcific thickening near the hilum. There were two anemic splenic infarcts distal to these occlusions, 5 cm. in diameter, which were partially calcified.

The lungs weighed 1300 gm. Distributed in the periphery of all three lobes of the right lung there were six triangular, sharply circumscribed, firm, yellowish, gritty, calcific infarcts (Figs. 6 and 7). Calcified thrombi were found occluding the pulmonary arteries supplying two of these areas (Fig. 6). Roentgenologic examination revealed slightly diffuse calcification in the remainder of the right and left lungs. No tumor was present.

The liver weighed 1590 gm. and in the left lobe there was a solitary, gray, circumscribed soft tumor mass, measuring 4 by 4 by 5 cm. (Fig. 10). Roentgenologic examination failed to reveal calcification in the tumor or in hepatic vessels. The pancreas weighed 159 gm. and was of unusually firm consistency. Section revealed many focal cystic areas up to 1 cm. in diameter scattered throughout. The ducts and ampulla of Vater were normal. The gastric mucosa was thickened and granular, with prominent rugal folds (Fig. 13). The granularity was due to diffuse calcium deposition throughout all areas as revealed by roentgenologic examination. The remainder of the gastro-intestinal tract was unchanged.

The kidneys weighed 130 gm. each and the capsules stripped with difficulty from finely granular surfaces with numerous large depressed scars (Fig. 17). Sections revealed a diffuse mottling in the cortex and linear streaks of calcium in the medulla (Fig. 18). The medulla was firm and contained numerous cystic areas from 7 to 8 mm. in diameter. The pelves were normal. The renal arteries were calcified and rigid but the lumina were not significantly narrowed. Roentgenograms confirmed the calcium distribution (Fig. 19).

The vertebral bodies contained numerous brown cysts up to 5 mm. in size in the midportion, whereas the remainder of each vertebral body was firm and dense (Fig. 22). The ribs were soft and fractured easily. On section, extensive fibrosis of the marrow was seen and cystic areas surrounded by dense elastic bone tissue were present (Fig. 23). The calvarium was soft and elastic but no cysts were found. The cortex of the femur was of normal thickness but much softer than is normal.

The right adrenal weighed 15 gm. and the left, 10 gm. The adrenals were not unusual except for the presence of two small cortical adenomata in each.

The brain and the remaining organs were unchanged.

Microscopic Examination

Neoplastic tissue was found microscopically in the liver, a left supraclavicular lymph node, and in the left sternocleidomastoid muscle in the region of the surgical incision (Figs. 11 and 12). In all areas the tumor was similar and consisted of sheets and cords of cells of uniform size, closely resembling chief cells. The rounded nuclei contained a diffuse chromatin network; mitotic figures were uncommon. In some areas the cells contained abnormal nuclei. The cytoplasm was abundant, eosinophilic, slightly granular, and contained a moderate amount of glycogen. A few cysts filled with eosinophilic material were noted.

The smaller branches of the coronary arteries revealed diffuse medial calcification without significant intimal proliferation. Calcium was deposited also on the elastic membranes of some arterioles (Fig. 3). Occasional myocardial fibers stained lavender with hematoxylin and eosin and were surrounded by slight interstitial fibrosis. Microscopic sections disclosed calcification of the annulus fibrosus of the mitral ring and of the tips of the papillary muscles. There was moderate serous atrophy of epicardial fat.

The mesenteric arteries, splenic artery, pancreaticoduodenal artery, gastric arteries, brachial and femoral arteries, as well as small vessels in skeletal muscle showed medial calcification and intimal fibrosis in varying degrees (Figs. 4 and 5). In branches of the pancreaticoduodenal, mesenteric, and splenic arteries, and in a small vessel in the interventricular septum of the heart, the medial calcification and intimal fibrosis significantly narrowed the vessel lumen. The lumina of the larger vessels, however, were widely patent.

Sections through the calcified infarcts revealed that the alveolar

spaces were completely filled with a loose vascular fibrous tissue. The alveolar walls were calcified and a calcific ring encircled the capillaries when viewed in cross section (Fig. 8). The occluding thrombi were partially organized and calcified. The remainder of the lung parenchyma showed patchy calcification of the alveolar walls. A considerable number of multinucleated giant cells and phagocytes often were adjacent to the calcium salts (Fig. 9). There was also calcification of some of the pulmonary arteries and veins, as well as of the bronchi.

There was focal and diffuse scarring of the kidneys. In the cortex many glomeruli were atrophic, fibrotic, and calcified. Many normal appearing glomeruli showed varying degrees of calcium deposition of the capillary basement membrane, Bowman's membrane, and of the efferent and afferent arterioles. Calcium deposits surrounded atrophic and normal proximal and distal tubules (Fig. 20). A considerable number of collecting tubules were dilated and many contained concentric masses of calcium (Fig. 21). A few neutrophils were found in some of the dilated tubules.

Throughout all areas of the stomach the gastric glands were greatly dilated and the mucosa thickened. The lumina of the glands were greatly distended with lamellated masses of inspissated secretion, often partially calcified (Fig. 14). In addition the interstitial tissue was partially calcified. Calcification of individual cells was not present.

The marrow spaces were filled with loose vascular fibrous tissue containing scattered giant cells and hemosiderin-laden macrophages (Fig. 24). The areas of increased density surrounding cystic lesions in the ribs were composed of an increased number of irregular bony trabeculae separated by marked marrow fibrosis. The trabeculae were poorly calcified, had a serrated outline due to osteoclastic resorption, and many were devoid of normal lamellar structure. Some trabeculae showed osteoclasts on one surface and rows of osteoblasts on the opposite surface (Fig. 25). The central areas of the vertebrae contained active marrow, whereas the outer areas showed marrow fibrosis and bony trabeculae as described above. The calvarium was similar.

There was marked pancreatic atrophy with interstitial fibrosis, together with much lymphocytic and a smaller amount of neutrophilic infiltration. Many dilated ducts of medium size contained calcified débris and concentric masses of eosinophilic material, probably inspissated secretion (Fig. 16). The islands of Langerhans were normal. Many muscular arteries showed extensive medial calcification and intimal fibrosis.

Sections from all three right parathyroid glands showed a marked

increase in fibrous tissue, often with isolation of groups of glandular cells. Chief cells composed the bulk of the parenchymal tissue. Many small vesicles filled with a pink colloid material were present (Fig. 15).

The zona reticularis and zona fasciculata were markedly vacuolated due to lipid deposition. The adenomata were composed of normal cortical cells. The medulla was normal.

Diagnoses

The final diagnoses were as follows: Resected carcinoma of the left parathyroid gland with metastases in left lung; metastatic carcinoma in left sternocleidomastoid muscle, left supraclavicular lymph node, and liver; extensive metastatic calcification of the lungs, kidneys, stomach, arteries, and heart; calcific occlusion of splenic arteries with splenic infarction; thrombosis of pulmonary arteries with pulmonary infarction and calcification; generalized osteitis fibrosa cystica involving the ribs, sternum, vertebrae, femur, and calvarium; fibrosis and slight atrophy of right parathyroid glands; chronic interstitial pancreatitis; cortical adenomata of the adrenal glands.

Discussion

In contrast with the paucity of reported cases of metastatic carcinoma of the parathyroid glands, Norris,[1] in 1947, cited 322 cases of adenoma, and Black and Ackerman,[2] in 1950, added 22 cases to the literature. Previously the only reported cases of functioning parathyroid carcinoma with distant metastases which had been carefully studied both clinically and post mortem were those of Meyer and Ragins[3] and of King and Wood.[4] Several cases, however, have been reported with local recurrence and with either infiltration or regional lymph node metastasis.[2,5-8] In the present case the tumor was obviously malignant as evidenced by local recurrence, regional lymphatic extension, and metastases in lung and liver. It is noteworthy, however, that microscopically it was not possible to distinguish this carcinoma from the parathyroid adenomas reported in the literature.[1,2,9]

The changes of generalized osteitis fibrosa cystica were entirely typical, but less extensive than those reported in several other cases.[10-12]

The extreme degree of medial calcification of the arterial system was most interesting and the functional results of arterial insufficiency have not been emphasized previously, although somewhat similar findings were reported in 1936 by Magnus and Scott[13] in a case of chronic nephritis with parathyroid hyperplasia and extensive pathologic calcification of the peripheral arteries. The influence of testosterone and estrogen therapy on the degree of soft tissue calcification cannot be

assessed. It is of interest to note, however, that the institution of this treatment was followed by significant lowering of serum calcium and that the calcium deposit in arteries which had been only slightly evident in the roentgenograms in June, 1949, had become extreme in November, 1949, after 6 weeks of hormone treatment.

The degree of calcium deposition in areas normally supplied by pulmonary arteries which were thrombosed was much more extensive than in the remainder of the lung. The position, shape, and histologic appearance of these regions were consistent with calcification in areas of local tissue damage or infarction. The degree of alveolar calcification in the remainder of the lungs was similar to that described in other cases.[10,14] No carcinoma was demonstrated in the lungs and the opacities interpreted clinically as carcinoma were in all probability attributable to the calcified infarcts.

Renal calcification was limited to the parenchymal tissue and was not accompanied by the formation of calculi. Functional renal impairment was evident clinically, but, despite the massive calcification and extensive interstitial and glomerular sclerosis, never led to obvious uremia. The calcium deposit was present to some degree in and about all segments of the tubules, the glomeruli, arteries, and arterioles. Roentgenologic examination, however, revealed a greater concentration in the medulla than in the cortex.

Myocardial degeneration is a very striking change in experimental animals dying of excessive doses of parathormone.[15,16] Here the morphologic findings were rather inconspicuous, consisting of calcification, degeneration of scattered myocardial fibers, and focal fibrosis. Calcification of chordae tendineae also has been noted in animals given excessive doses of parathormone.[16]

Metastatic calcification of the stomach usually affects the distal or acid-bearing portion, although in the present case there was diffuse calcium deposition in all areas. Microscopically, calcification of the interstitial tissue and glandular cells has been emphasized hitherto; no cases have been found with the degree of dilatation and calcification of the mass of contained secretion found in this case.

The diffuse fibrosis and slight atrophy of the three remaining parathyroid glands deserve mentioning. It is questionable whether these changes were due to surgical trauma, to an involutionary change resulting from hypersecretion of parathyroid hormone by the tumor cells, or to some other cause. In this relation it is noteworthy that Jaffe and Bodansky [17] described functional involutional atrophy of the parathyroid glands in dogs dying of induced acute hyperparathyroidism, while McJunkin, Tweedy, and Breuhaus [18] found that para-

thyroid hormone inhibited mitotic activity of parathyroid cells when given to rats in amounts insufficient to produce hypercalcemia and destructive lesions of parenchymatous organs.

Summary

In a case of metastasizing carcinoma of the parathyroid gland with osteitis fibrosa cystica and extensive calcinosis, the tumors removed surgically from the neck and lung and those found post mortem in the sternocleidomastoid muscle and liver were alike in histologic appearance. They were composed for the most part of well differentiated cells resembling chief cells, which could not be differentiated by morphologic criteria from the elements of growths generally diagnosed as parathyroid adenomas.

Three remaining parathyroid glands were neither neoplastic nor hyperplastic, but showed fibrosis and atrophy. The possibility was considered that this may have been an involutionary change resulting from hypersecretion of parathyroid hormone by the neoplastic cells.

Osteitis fibrosa cystica was generalized but less extensive than in a number of previously reported cases of hyperparathyroidism.

Other features were a very marked degree of medial calcification of arteries of medium and small size, associated clinically with pallor, cyanosis, and circulatory insufficiency of the extremities; extensive deposition of calcium in infarcted areas of the lungs; widespread renal calcinosis without obvious nephrolithiasis or renal failure; and metastatic calcification of the gastric mucosa, which was not limited to cells engaged in acid secretion.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 70

FIG. 1. Roentgenograms of chest (A) taken on July 5, 1949, shortly after admission, showing indistinctly in the left lung two discrete areas which were shown to be carcinomatous metastases; (B) taken on October 22, 1949, showing extensive opacity.

A

B

1

Ellis and Barr

Carcinoma of the Parathyroid Gland

PLATE 71

FIG. 2. Roentgenogram, showing diffuse calcification of the superior mesenteric artery and its branches.

FIG. 3. Calcification of elastica of arteriole of heart. Hematoxylin and eosin stain. × 1260.

FIG. 4. Medial calcification and intimal fibrosis of mesenteric artery. Hematoxylin and eosin stain. × 140.

FIG. 5. Calcification of media of small artery in skeletal muscle. Hematoxylin and eosin stain. × 190.

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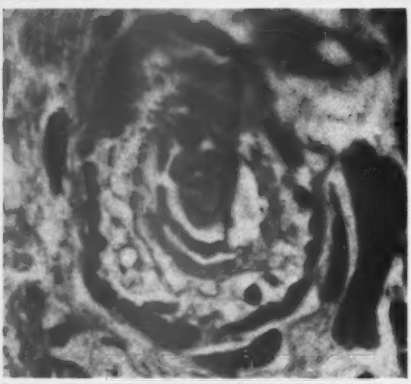

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Carcinoma of the Parathyroid Gland

PLATE 72

FIG. 6. Thrombus in a branch of the pulmonary artery, with pyramidal area of calcification in the distribution of the artery.

FIG. 7. Higher magnification of another calcified infarct. There is emphysema and moderate calcification of adjacent lung parenchyma.

FIG. 8. Organizing infarct showing calcification largely restricted to alveolar walls and capillaries. Hematoxylin and eosin stain. × 180.

FIG. 9. Calcification of the type found scattered diffusely throughout the lungs. Of note are the multinucleated giant cell reaction and the alveolar fibrosis. Hematoxylin and eosin stain. × 120.

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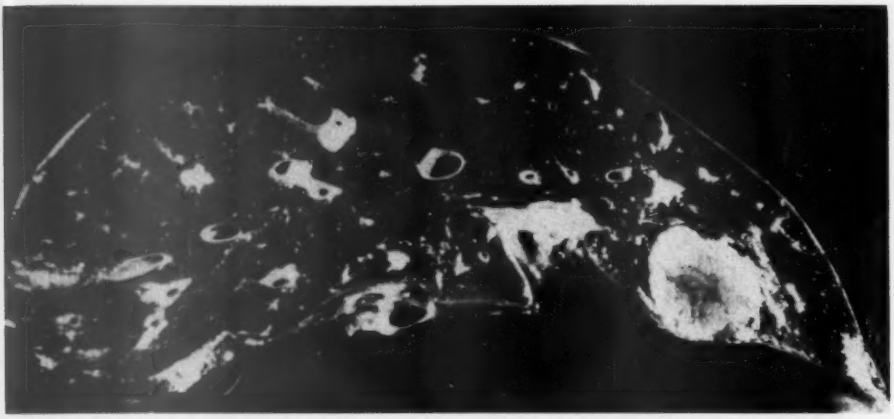
Carcinoma of the Parathyroid Gland

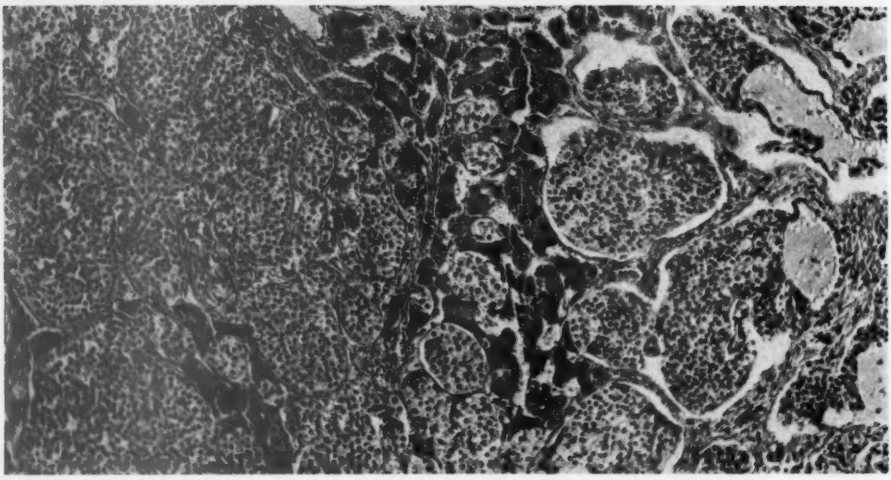
PLATE 73

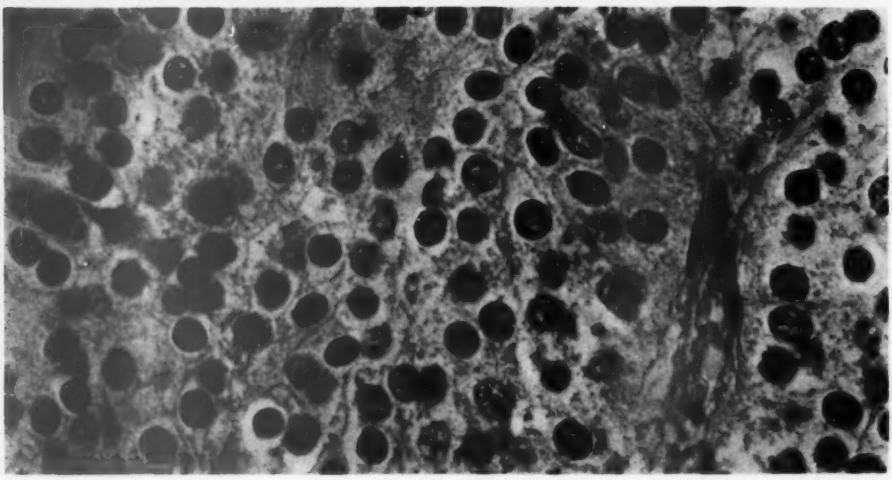
FIG. 10. Solitary, circumscribed metastasis of carcinoma in the left lobe of liver.

FIG. 11. Microscopic detail of the margin of the hepatic metastasis, showing colloid-filled spaces at the right. Hematoxylin and eosin stain. × 130.

FIG. 12. Higher power of carcinoma in left supraclavicular lymph node. Hematoxylin and eosin stain. × 800.







Ellis and Barr Carcinoma of the Parathyroid Gland

PLATE 74

FIG. 13. Mucosa of stomach showing coarsened rugal pattern with fine granularity due to plugging of glands with calcified material.

FIG. 14. Dilatation of gastric glands containing calcified débris and secretion. There is moderate calcification of interstitial connective tissue between the glands. Hematoxylin and eosin stain. × 50.

FIG. 15. Fibrosis and slight atrophy of one of the remaining parathyroid glands. Hematoxylin and eosin stain. × 800.

FIG. 16. Dilatation of pancreatic ducts containing lamellated contents. There is marked interstitial fibrosis of the surrounding glandular tissues, with infiltration by lymphocytes. Hematoxylin and eosin stain. × 50.

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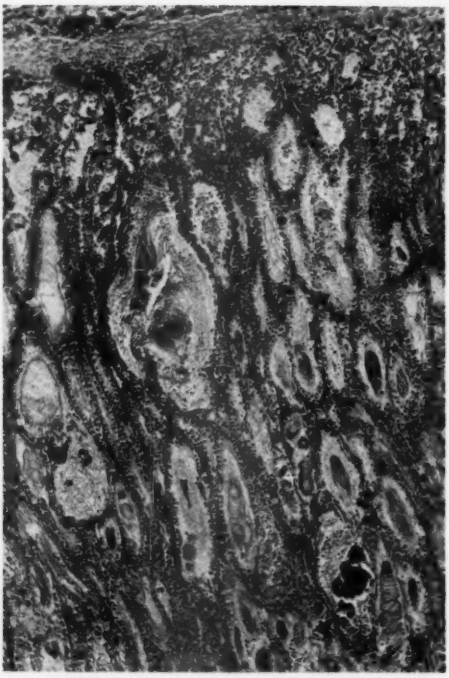
El



Ellis and Barr

Carcinoma of the Parathyroid Gland

Plate 75

Fig. 17. Diffuse granularity of kidney surface, with larger depressed scars at the upper pole.

Fig. 18. Cut surface of kidney illustrating diffuse cortical calcification, linear streaks of calcium in medullary rays, and medullary cysts. The renal pelvis is normal.

Fig. 19. Roentgenogram of kidney. Calcium deposition is greatest in medulla. The renal arteries are diffusely outlined by calcium.

Fig. 20. Calcification of glomerular arterioles, Bowman's membrane, and peritubular membranes, with occlusion of tubules by calcium. Von Kossa's stain. × 180.

Fig. 21. Concentric masses of calcium in renal medulla, with tubular dilatation and interstitial fibrosis. Hematoxylin and eosin stain. × 50.

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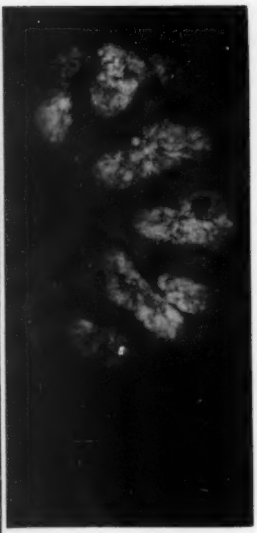

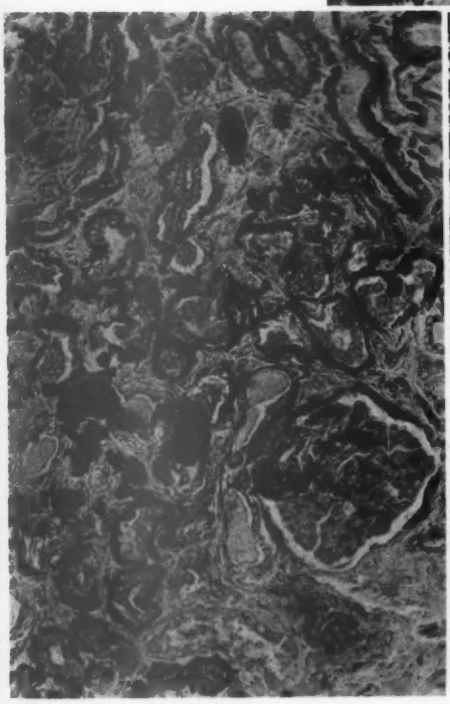

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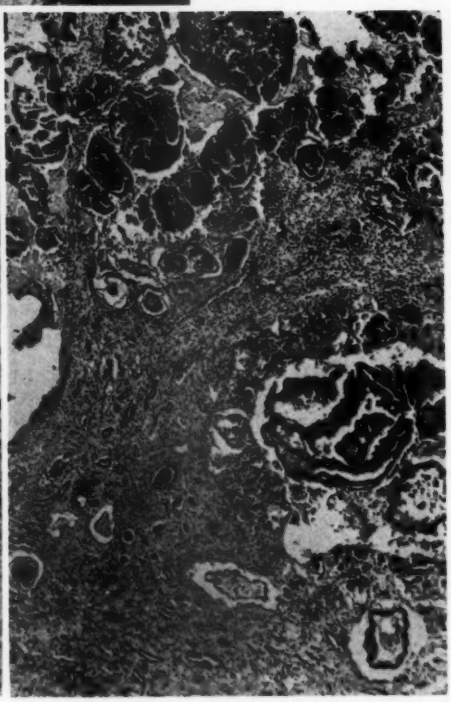

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Carcinoma of the Parathyroid Gland

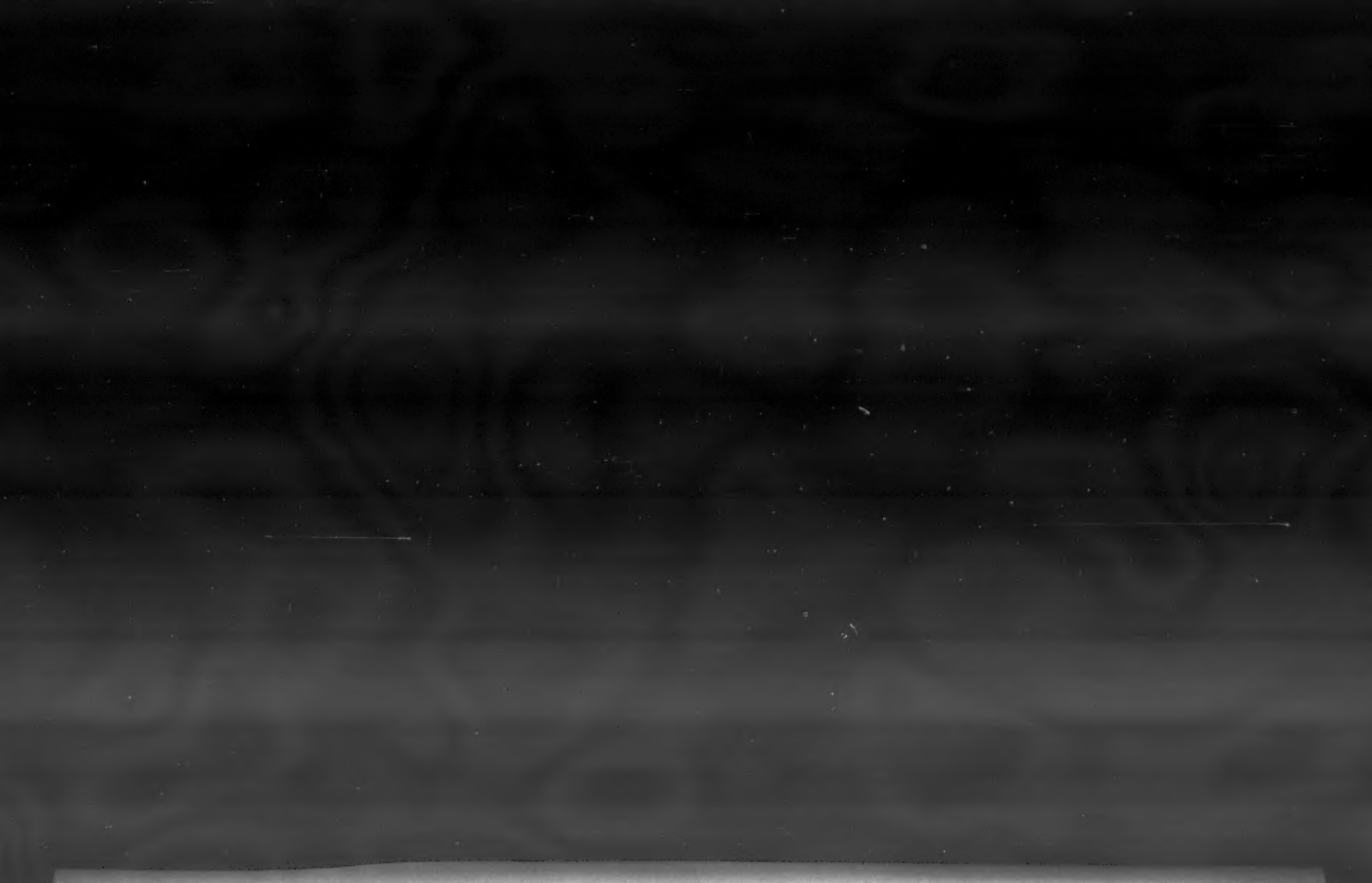
PLATE 76

FIG. 22. Roentgenograms of vertebrae. Osteoporosis with disappearance of central trabeculae and condensation of remainder of the vertebral body.

FIG. 23. Roentgenogram of rib illustrating multiple areas of cyst formation.

FIG. 24. Rib. Resorption of old bone with complete fibrosis of the marrow spaces. Hematoxylin and eosin stain. × 50.

FIG. 25. Vertebra. Bony trabeculae undergoing absorption. Narrow bridge of new bone with absence of lamellar pattern surfaced on lower side by syncytial osteoclastic giant cells and on the upper side by proliferating osteoblasts. Hematoxylin and eosin stain. × 280.



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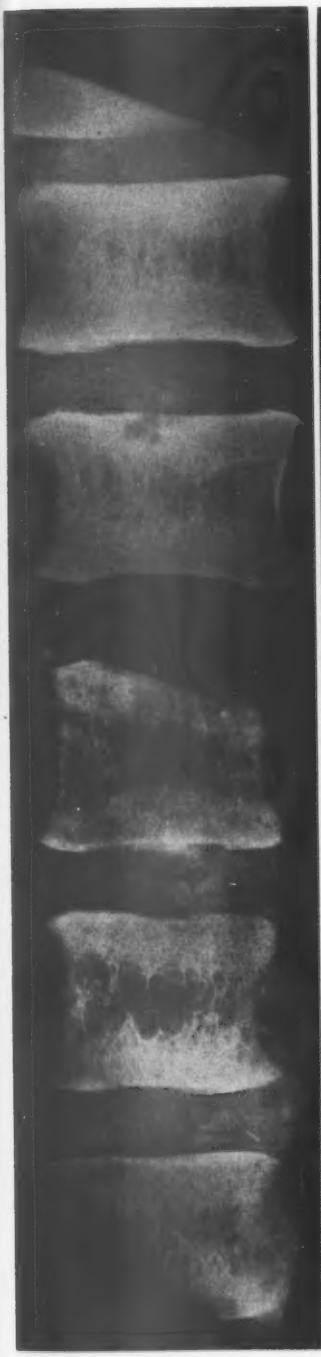

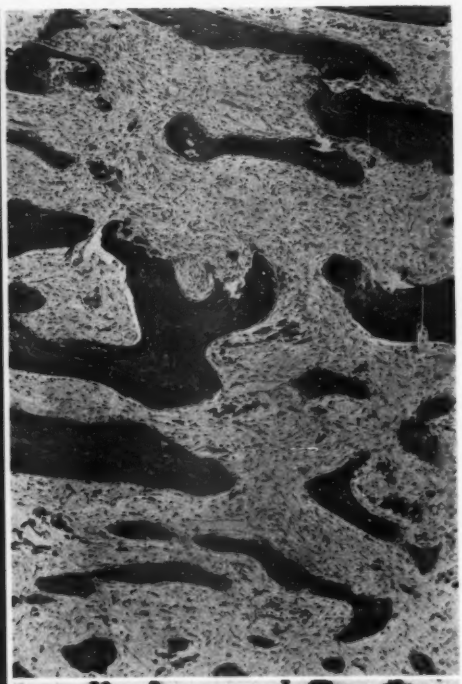

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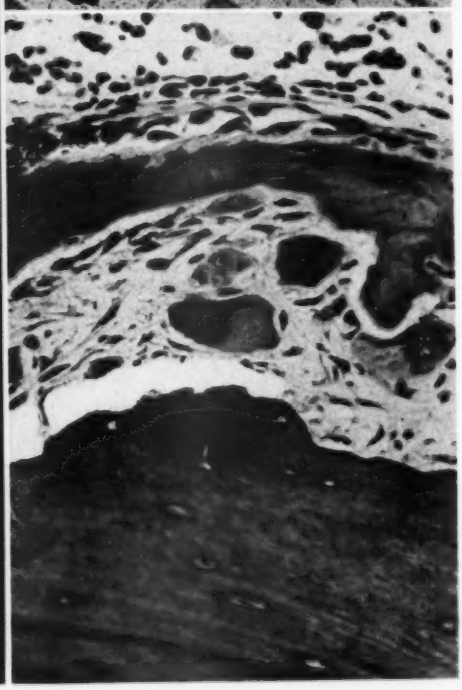

25

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Carcinoma of the Parathyroid Gland

BONE MARROW EMBOLISM *

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Fragments of bone marrow in the pulmonary circulation have been observed only rarely in man. Emboli of this origin usually are encountered in the medium-sized and small branches of the pulmonary arteries. Bone marrow embolism is to be distinguished from fat embolism in which extracellular fat, usually set free from marrow fat cells, enters the blood stream, occluding the capillaries and small arteries of the pulmonary and systemic circulation. In the majority of cases in which bone marrow emboli have been observed fractures could be demonstrated, and in most of the remaining cases the circumstances of death strongly suggested that fractures existed but were not detected.

Bone marrow emboli within branches of the pulmonary arteries were first observed in man and in experimental animals by Lubarsch [1] and his associate Lengemann,[2] and were reported by the latter in his inaugural dissertation (1897). At approximately the same time Maximow [3] independently reported identical emboli in rabbits killed by destruction of the medulla oblongata. He attributed the bone marrow embolism to fragmentation of bone at the base of the skull and possibly of vertebrae during this procedure. He obtained similar results by intentionally fracturing the occipital bone of rabbits with hammer and chisel or by killing the animals with blows on the neck. He failed to find bone marrow embolism when he killed the animal by a mixture of chloroform and curare or by sudden severance of the head, avoiding any concussion of the skeletal system. From these and other experiments he concluded that bone marrow embolism was due to fracture of cancellous bone.

Lubarsch,[1,4] taking issue with Maximow's concept,[3] maintained that bone marrow embolism occurs only exceptionally as the result of trauma alone. As predisposing factors he suggested (1) alteration of the bone marrow characterized by severe hyperemia, softening and decreased cohesiveness of its cellular elements, and (2) concussion of the skeletal system not necessarily associated with fracture. In sup-

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port of this concept he mentioned the occurrence of bone marrow embolism in 4 cases of eclampsia, 2 of which were more fully reported by Lengemann [2] (1897), and in rabbits which had received intravenous injections of ground liver, kidney, or placental tissue. He maintained that in both the experimental animals so treated and women with eclampsia there was an alteration of the bone marrow which manifested itself regularly by extensive embolization of megakaryocytes and in some instances by the presence of ecchymoses in the bone marrow. He pointed out, however, that in man the additional concussion of the bone, such as that produced by eclamptic convulsions, might be necessary for the occurrence of bone marrow embolism. Although Lubarsch was inclined to regard the changes in the bone marrow itself as more important than the concussion, he pointed out that only careful and continued investigation of the lungs in cases of traumatic death would permit a decision in this respect.

Subsequently, Lengemann [5] (1901) emphasized even more strongly the importance of concussion of bone, both in man and in experimental animals. Although he still maintained that alteration of bone marrow was the predisposing factor, he considered the violent defensive movements of the rabbits during manipulation and their agonal twitchings sufficient to produce concussion of bone with subsequent hemorrhage and detachment of marrow fragments.

Few additional reports have appeared in the literature. Wuttig [6] produced bone marrow embolism in rabbits by instrumental fragmentation of the femurs, and Ogata [7] achieved similar results by dropping 1 month old animals several times from the height of 1 meter upon a wooden surface. Ogata attributed the displacement of marrow fragments to concussion of bone leading to tearing of the marrow, without postulating the occurrence of fractures. He suggested that "unintentional" trauma, such as violent tapping with the hind limbs upon hard surfaces, may explain the presence of bone marrow emboli in rabbits used for a variety of other experiments. Bilancioni [8] also reported the incidental finding of bone marrow embolism in an albino rabbit. Lauche [9] made a similar observation in an Ethiopian ground squirrel (*Xerus rutilus*), submitted to him from the Berlin zoo. No evidence of fracture was apparent at necropsy, but extensive fat embolism in the lungs suggested that the animal had incurred trauma of some type and that fractures might have escaped detection.

Additional cases in man were reported by Sotti,[10] Karlén,[11] Schenken and Coleman,[12] and Lindsay and Moon.[13] Of particular interest is Karlén's report of extensive bone marrow and fat embolism in a patient

who had severe generalized convulsions following myelography, probably on the basis of hypersensitivity to the contrast medium (perabrodil). The author suggested that embolism may have been due to undetected fractures of the vertebrae caused by the convulsions. Since vertebral fractures were not suspected at necropsy, meticulous examination of each vertebra was not performed; however, an extensive retroperitoneal hemorrhage which was present may well have resulted from fracture of the spine, although Karlén did not suggest this possibility. Warren [14] mentioned that among 100 cases of fat embolism he found 3 in which the pulmonary arteries also contained fragments of bone marrow.

Thus, search of the literature revealed a total of 8 cases of bone marrow embolism reported with some clinical data. These are summarized in Table I. Five additional instances (2 of Lubarsch and 3 of Warren) were mentioned but not reported in detail, bringing the total number of recorded cases to 13.

Material and Methods

The present study is based upon the clinical and pathologic data from cases of bone marrow embolism in the files of the Armed Forces Institute of Pathology. In the 2 cases first observed by us at the Veterans Administration Hospital, Washington, D.C., both lungs were still available for examination after discovery of bone marrow emboli in routine sections. These lungs were systematically examined, and the extent, distribution, and severity of bone marrow embolism were determined by the study of multiple sections from each lobe and large representative sections of entire lobes. Five additional cases with the diagnosis of bone marrow embolism were found in the files of the Armed Forces Institute of Pathology. The remaining 20 were brought to light by a systematic survey of cases in which death followed trauma with multiple fractures, accidental electrocution, and generalized convulsions. Fatal cases of eclampsia, tetanus, and instances in which death followed convulsion treatment of mental disorders were selected as examples of post-convulsive death. Examination of microscopic sections of the lungs in a control series of 240 consecutive cases necropsied at the Veterans Administration Hospital in Washington failed to disclose an unequivocal case of bone marrow embolism. One to six sections of lung stained with hematoxylin and eosin were available, with an average of approximately two sections per case in the investigated group and three in the control group. When the original sections were technically poor or contained structures strongly suggestive of,

but not definitely identifiable as, bone marrow emboli, additional sections were taken if wet tissue blocks were available. Wherever possible, frozen sections of lung, kidney, and brain were stained for neutral fat in order to determine the presence and severity or absence of associated fat embolism.

Histologic Observations

Unlike fat embolism which often can be recognized grossly, bone marrow embolism can be diagnosed only on microscopic examination. In all cases of our series medium-sized and small branches of the pulmonary artery were either partly or completely occluded by marrow fragments (Figs. 1 to 5, 7 and 8). Very small bone marrow emboli

Table I

Reported Cases of Bone Marrow Embolism

Author	Year	Age	Sex	Trauma	Fracture	Time interval between trauma and death	Associated fat embolism
Lengemann[2]	1897	21	F	Generalized convulsions (eclampsia)	Not observed	8-24 hours*	Not reported
Lengemann[3]	1897	25	F	Generalized convulsions (eclampsia)	Not observed	5 days†	Not reported
Sotti[10]	1910	78	F	Not observed	Not observed		Not reported
Karlén[11]	1942	35	M	Generalized convulsions (drug hypersensitivity)	Not observed	2 days	Lung, kidney, brain
Schenken and Coleman[12]	1943	86	F	Fall, open reduction of fracture	Neck of left femur	4-5 days	Lung (severe), kidney
Lindsay and Moon[13]	1946	21	M	Fall from moving train, generalized convulsions (cerebral hemorrhage)	Lateral condyle, right femur; others?	39 hours	Lung (severe)
Lindsay and Moon[13]	1946	45	M	Strangled, thrown down cliff	Skull, sternum, left clavicle, mandible, right radius, ribs, 7th thoracic vertebra	Less than 24 hours‡	Lung (mild)
Lindsay and Moon[13]	1946	23	M	Motorcycle accident	Skull, sternum, left radius, ulna and femur, right tibia and fibula	Few minutes	None

* Ten eclamptic convulsions on the day of delivery. Died 8 hours following delivery.
† Death 5 days following first attack of convulsion; had a total of 9 convulsions.
‡ Was dead when body was discovered the morning after the incident.

were observed in interalveolar capillaries (Fig. 11) in cases in which arterial embolization was extensive; in one of these, occasional minute bone marrow emboli were found also in capillaries of the brain (Fig. 12). In one instance a bone marrow fragment was lodged in one of the recesses between the pectinate muscles of the right auricle of the heart (Fig. 14).

The completely occluded arterial branches varied in diameter, the largest observed being 520 μ. Large sections of entire lobes revealed that most of the embolized vessels were located within 3 cm. of the pleural surface. Sections including the pleura were thus more likely to show marrow emboli than those taken close to the hilum. In one case, a large section from the right lower lobe revealed two marrow fragments measuring 250 and 450 μ in diameter, respectively, free in the lumen of a large artery near the hilum. Death in this case occurred only a few minutes after the trauma.

The embolized marrow fragments had, as a rule, the characteristic appearance of normal bone marrow and were histologically identical with the patient's vertebral and sternal marrow whenever such material was available for comparison. The relative proportion of fat cells and myeloid cells varied. Myeloid cells of all types were observed, although not always in the same fragment. The presence of eosinophilic myelocytes, foci of normoblasts, and megakaryocytes (Fig. 4) made the recognition of marrow fragments particularly easy. Individual megakaryocytes entrapped in capillaries were, of course, not considered to be diagnostic of bone marrow embolism. Macrophages laden with blood pigment sometimes were encountered. Unusual findings included a group of arterioles within an embolized marrow fragment (Fig. 9) in one instance, and fragments of bone trabeculae in two. One bone spicule was present in the center of a relatively large bone marrow embolus (Fig. 5), while other intravascular bone fragments were almost completely devoid of marrow elements (Fig. 6). Such intravascular bone fragments in association with bone marrow emboli have been described in a rabbit by Maximow,[3] but have not been reported in man. While as a rule no difficulty was experienced in recognizing bone marrow emboli in arteries, the arterioles and capillaries sometimes contained tissue fragments composed of one or two fat cells with very few or no myeloid elements. Recognition of the cell borders of fat cells and definite myeloid cells sometimes made it possible to identify these small fragments as bone marrow emboli. When this could not be done, the case was eliminated unless additional sections revealed unequivocal evidence of bone marrow embolism (Figs. 10 and 11).

There is nothing to suggest that intravascular fragments of bone marrow may represent foci of metaplasia or artifacts. Lengemann [2] was able to rule out the latter possibility in rabbits on the basis of his experimental studies. Our observations in human material convinced us that the presence of bone marrow fragments in the lumina of arteries can be explained by no other mechanism than embolization of displaced marrow. The tissue fragments were found always in arteries, never in veins, bronchi, or alveoli. In incompletely occluded arteries the portion of the lumen not occupied by bone marrow emboli sometimes contained a recent thrombus (Fig. 8). At sites of bifurcation of arteries the emboli were completely molded to the shape of the dividing vessels and presented the appearance of "riding" emboli (Fig. 7). The walls of completely occluded arteries often were thinned out, which suggested that the arteries had been distended by marrow fragments having a diameter greater than that of the original lumen, an observation previously recorded by Maximow.[3] The shape of the emboli and the thinned walls of the arteries indicated that the tissue fragments were forced into branches of the pulmonary artery by the propelling power of cardiac action and lodged where the resistance of the distended vascular walls could no longer be overcome by the intra-arterial pressure.

In several instances degenerative changes were observed in embolized marrow fragments. In one case there was evidence of early necrosis of fat tissue. In 3 other instances the free margin of the embolus was lined with endothelial cells and evidence of fibroblastic proliferation was noted immediately beneath the endothelial lining (Fig. 13). Fat-laden macrophages were scattered among the fat cells. Inflammatory infiltrations in the vessel walls were not observed in our material nor reported in the literature.

Clinical Observations

The significant data pertaining to the cases which form the basis of this study are summarized in Tables II and III. Of the 27 cases, 18 were instances of post-traumatic death, 2 of accidental electrocution, and 7 of death following severe generalized convulsions. In 3 cases these convulsions were induced by insulin or electric shock used in the treatment of dementia praecox. The remaining 4 cases included one of eclampsia, one of tetanus, one of congestive heart failure due to rheumatic valvular disease in which the convulsions were probably caused by cerebral edema, and one case in which generalized clonic and tonic convulsions followed shortly after topical application of cocaine and pontocaine preparatory to bronchoscopy.

Illustrative Cases

Case 10

A white male, 74 years old, was admitted to the hospital for treatment of a metastatic squamous cell carcinoma of the cervical lymph nodes, both lungs, and the left pleura. He was ambulatory. The patient fell in the bathroom and hit his head. The nurse heard the fall and rushed to him. He spoke to her, then immediately lapsed into unconsciousness. His pulse could not be obtained. When seen by a doctor a few minutes later, he had ceased to breathe and was cyanotic. He did not respond to artificial respiration and oxygen and was pronounced dead 10 minutes after the accident.

Post-mortem examination revealed metastatic carcinoma of the cervical and intrathoracic lymph nodes, thyroid, lungs, and pleura. Microscopic examination of the lungs showed numerous marrow emboli in 11 of 15 sections taken from all lobes. No fat embolism was found in sections of lung, brain, and kidney.

Comment. In this case of massive bone marrow embolism there were no other post-mortem changes to account for the relatively sudden death of the patient. No fracture was demonstrated. The spine, however, was not examined in detail, no vertebral fractures having been suspected by the prosector. This case not only indicates that bone marrow embolism may be extensive and severe, even in instances in which only a relatively short time elapses between trauma and death, but it also suggests that bone marrow embolism may be the only available evidence of fracture and thus on occasion may be of medicolegal significance in determining the circumstances of an otherwise unexplained death.

Case 26

A white male, 48 years old, was known to have had rheumatic heart disease since 1941. Congestive heart failure developed about 1 year before his admission to the hospital in April, 1949. On April 12, he had an attack of acute pulmonary edema. At noon on April 15 a nurse entered the patient's room and found him in a convulsion which lasted at least 1 minute. There was generalized clonus, apnea, and cyanosis. The pulse could not be felt and the heart sounds were too faint to be counted; the blood pressure was 88/78 mm. of Hg. The lungs were full of moist râles and moderately coarse rhonchi. The patient regained consciousness 20 minutes later, following administration of morphine and withdrawal of 250 cc. of blood; blood pressure rose to 110/80; pulse was 110 and irregular. Pulmonary râles diminished considerably and cyanosis and dyspnea disappeared upon administration of oxygen. The patient gradually improved and appeared to be fairly comfortable for the following 2 days. At 9:00 a.m. on April 17, the patient's blood pressure could not be obtained. He was dyspneic and cyanotic and was coughing up bloody sputum. Respirations became Cheyne-Stokes in character, gasping in type, and had slowed to 12 per minute by 10:30 a.m. The patient was pronounced dead 10 minutes later.

Post-mortem examination revealed evidence of old rheumatic heart disease with involvement of mitral, aortic, and tricuspid valves, rheumatic myocarditis, mural thrombi of right and left auricles, and multi-

TABLE II

Pulmonary Bone Marrow Embolism in Cases of Traumatic Death

Case no.	A.F.I.P. acc. no.	Age and sex	Type of trauma or accident	Fracture	Time interval between trauma and death	Number of sections of lung		Associated fat embolism
						Available	Positive for B.M.E.*	
1	72964	77 F	Hip injury	Femur (intertrochanteric)	2 weeks (?) (history unreliable)	6	1†	Lung (mild)
2	108359	22 M	Airplane crash	Pelvis, femur	49 hours	4	1	Lung (severe)
3	112369	24 M	Truck accident	Pelvis, femur, sacrum	22 hours	1	1	None
4	112406	20–25 M	Airplane crash	Skull, tibia, fibula	Not known (found dead in wreckage)	3	1	Not determined
5	114729	32 M	Glider crash	Humerus, rib, metatarsal bones	10 minutes	5	2	Lung (moderate)
6	115117	22 M	Glider crash	Tibia, fibula, carpal and tarsal bones	12 hours	5	2	Lung (severe), kidney
7	119827	25 M	Dive into shallow water	5th and 6th cervical vertebrae	Few minutes	3	1	None
8	125081	21 M	Auto accident	Pelvis, 3rd and 4th lumbar vertebrae (compression)	Few seconds or minutes	3	1	Not determined
9	167345	26 M	Truck accident	Skull, ulna	26 hours	4	1	Lung (mild)
10	192095	74 M	Fall, hitting head	Not detected	Few minutes	15	11	None
11	192264	22 M	Airplane crash	Sternum, ribs	Not known	1	1	Not determined
12	196504	28 M	Auto accident	6th and 7th cervical vertebrae	19 hours	6	4	Not determined
13	198173	24 M	Auto accident	Rib, femur, mandible	Several hours	2	1	None
14	202303	20 M	25 ft. fall from cliff	4th thoracic vertebra (compression), ribs	24 hours	1	1	Not determined
15	261190	18 M	Auto accident	1st and 2nd cervical vertebrae, occipital bone (basilar portion)	42 hours	4	4	Lung (mild)

16	268516	20 M	Dive into shallow water	4th and 5th cervical vertebrae	?	4	1	None
17	269555	66 M	?‡	?	?	5	5§	Lung (severe), kidney, heart, brain
18	281817	20 M	Airplane crash	Humerus	? (Body found in wreckage)	4	4	Lung (moderate)
19	156594	30 M	Accidental electrocution	?	?	2	2	None
20	237833	20 M	Accidental electrocution	?	5 hours	1	1	Lung (mild)

* B.M.E. = Bone marrow embolism.
† A single bone marrow embolus was found also in a section from the wall of the right auricle, entrapped in a recess between pectinate muscles.
‡ Debilitated patient who probably had senile osteoporosis. Trauma was not suspected until microscopic examination revealed extensive fat and bone marrow embolism.
§ Occasional intracapillary bone marrow emboli were found also in 2 of 3 sections of brain.

ple pulmonary infarcts. Sections from both lungs showed numerous bone marrow emboli. Occasional ones contained fragments of bone trabeculae (Figs. 5 and 6). There was fat embolism in the lungs, but none in brain, kidney, and heart.

Comment. This is the second case in which massive embolization by bone marrow fragments could be proved. Sections from every lobe contained bone marrow emboli. The finding of occasional bone spicules in marrow fragments is indicative of fracture, which in the absence of any evidence of external trauma can be attributed only to the convulsions. It was not possible to determine whether the pulmonary infarcts were secondary to bone marrow embolism or to pulmonary emboli originating from the mural thrombi of the heart. It was difficult also to decide what part bone marrow embolism played in precipitating the death of this patient. The extent and severity of the bone marrow embolism, however, suggest that it produced a significant impairment of the pulmonary circulation.

Case 27

A white male, 32 years old, with known active pulmonary tuberculosis was prepared for bronchoscopic examination. After a preliminary test failed to reveal evidence of cocaine sensitivity, the throat was sprayed with 3 per cent pontocaine and the epiglottis and vocal cords were topically anesthetized with 2 per cent cocaine solution. After the procedure the patient walked about the clinic for a few minutes, then sat in the waiting room. Within a short time generalized clonic

and tonic convulsions developed and he became extremely cyanotic and hyperpneic. After intravenous administration of sodium pentothal the convulsions stopped. Positive pressure oxygen was administered, but the cyanosis deepened and within a few minutes no signs of life could be elicited. Because several physicians thought that there was still an occasional heart beat, intrathoracic cardiac massage was tried. When the heart was exposed it was found to be extremely dilated. Neither cardiac massage nor intracardiac administration of adrenalin proved effective.

TABLE III

Cases of Bone Marrow Embolism Associated with Generalized Convulsions

Case no.	A.F.I.P. acc. no.	Age and sex	Cause or probable cause of convulsion	Time interval between convulsions and death	Number of sections of lung		Associated fat embolism
					Available	Positive for B.M.E.*	
21	126408	32 M	Tetanus	Less than 5 days	5	3	Lung (mild)
22	128359	20 M	Convulsive shock therapy	Less than 12 days	6	1	None
23	152063	22 M	Convulsive shock therapy	Less than 7 days	5	1	None
24	159159	21 M	Convulsive shock therapy	25–30 days	3	1	Not determined
25	204864	18 F	Eclampsia	Less than 42 hours	5	3	None
26	276915	48 M	Cerebral edema (?) due to congestive heart failure	49 hours	15	15	Lung (mild)
27	276108	32 M	Topical application of cocaine and pontocaine preparatory to bronchoscopy	Few minutes	8	6	Lung (moderate), brain (minimal)

* B.M.E. = Bone marrow embolism.

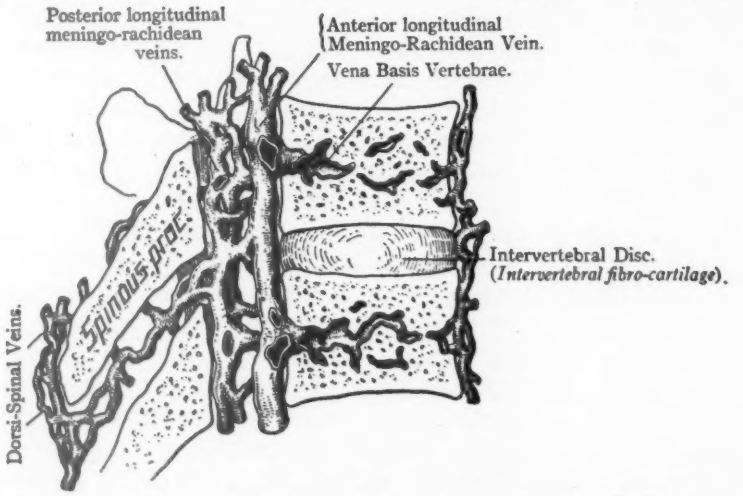
Post-mortem examination revealed active pulmonary tuberculosis involving the left upper lobe. Numerous bone marrow emboli were found in 6 of 8 sections from the lungs. There were, in addition, moderate fat embolism of the lungs and very occasional intravascular fat droplets in arterioles of the brain.

Comment. Both pontocaine and cocaine are known to produce severe toxic reactions associated with generalized convulsions in susceptible persons. In this case pulmonary bone marrow embolism probably was extensive since three-fourths of the sections from various lobes showed bone marrow emboli. The clinical symptoms appeared consistent with pulmonary embolism, and it is believed that the patient's failure to recover from the convulsive episode may have been due to the occlusion of medium-sized and small pulmonary vessels by

bone marrow fragments. Fat embolism also may have played a rôle, though a minor one, since it was much less extensive than bone marrow embolism.

Discussion

The anatomical structure of cancellous bone containing red marrow may account for the displacement of marrow fragments into the circulation following trauma. In this connection four factors seem to be of particular significance: (1) The marrow is separated by only a single layer of endothelial cells from the lumen of the intramedullary sinusoidal blood vessels, an anatomical relationship which permits ready access of fragments of marrow into the disrupted sinusoids. (2) The sinusoids communicate freely and widely with the veins which pass through cortical bone. (3) The diameters of these veins are great enough to permit passage of fragments of tissue of the size demonstrated in the lungs (Text-fig. 1). (4) These veins do not collapse since they are



Text-figure 1. The venous circulation of the vertebral bodies. Reproduced, by permission, from Deaver, J. B. Surgical Anatomy of the Human Body. P. Blakiston's Son & Co., Philadelphia, 1926, ed. 2, 2, 399.

firmly adherent to the bony channel as they penetrate the cortex. Some of these points were well illustrated by Wagoner and Pendergrass [15] in their study of the intrinsic circulation of the vertebrae. They demonstrated within the bodies of the lumbar vertebrae of man large and extensive intercommunicating venous spaces lined by a single layer of endothelial cells and frequently supported by bone trabeculae throughout a large portion of their circumference. It is obvious that

fragmentation of cancellous bone associated with hemorrhage will lead to tearing of the marrow and of the thin-walled venous sinusoids. Marrow fragments completely torn from their surroundings may then be forced into the disrupted sinusoids and from there into the vertebral veins by the increased local pressure produced by hemorrhage and edema. It is likely that in compression fractures of the vertebrae the local pressure may be enhanced by the very nature of the fracture.

Whether there must be actual fracture for the production of bone marrow embolism could not be established definitely from our material. The possibility that concussion of bone without disruption of its continuity may produce hemorrhage severe enough to lead to tearing and detachment of marrow fragments could not be ruled out but is considered unlikely. It is true that in 11 of the 27 cases of our series, and in 5 of 11 cases reported in the literature, no fractures were demonstrated. Of the 11 patients of our series, however, 7 had generalized convulsions prior to death, 2 died following accidental electrocution, one had a definite history of trauma, and in one extensive fat embolism was observed in addition to the bone marrow embolism, suggesting that fracture had occurred but had escaped detection. Generalized convulsions had occurred in 5 of the 6 cases without demonstrated fracture which have been reported in the literature. Four of these patients died of eclampsia and one had convulsions presumably caused by hypersensitivity to the contrast medium used for myelography.

That vertebral fractures occur during convulsions appears to be well established. In many of the reported cases the patients were asymptomatic and fractures remained undiagnosed until weeks or months later when deformities of the spine were discovered clinically or by roentgenologic examination. This was first observed by Lehndorff [16] in 1907 in a patient who survived tetanus. Changes demonstrated roentgenologically in such cases were subsequently described [17-19] and were considered to be attributable to vertebral fractures occurring during the convulsions. In a series of 21 patients,[17] 14 presented roentgenologic evidence of changes in the vertebrae after clinical recovery from tetanus. Four cases have been recorded in which vertebral fractures in patients who died from tetanus were actually demonstrated at necropsy.[20-23] Roentgenologic evidence of compression fractures of vertebrae has been reported also in patients undergoing convulsion treatment for psychoses [24-28] and following epileptic convulsions.[28,29] The incidence of such fractures in three series of patients receiving metrazol shock therapy ranged between 43.1 and 47 per cent.[25,27,28] Pearson and Ostrum [28] concluded that fractures of the spine may result from convulsions of any cause. The preponder-

ance of fractures of the anterior portions of the vertebral bodies after convulsions was attributed to sudden anterior flexion of the thoracic spine [27] which is due to the greater power of the spinal flexors as compared with the opposing extensors.

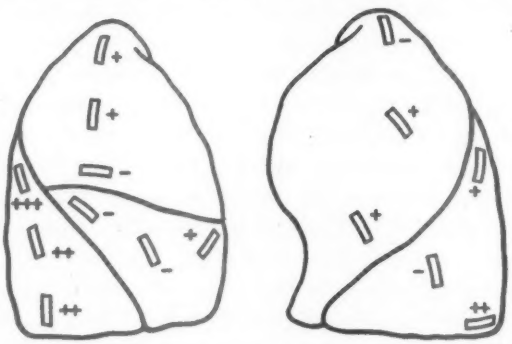
On the basis of these observations it is suggested that in those cases of our series in which convulsions preceded the patient's death, bone marrow embolism most probably was due to vertebral fractures. Detection of such fractures at necropsy demands careful examination of the spine, and it is unlikely that this was carried out in any of the cases of our series. It is quite probable also that the severe tetanic muscle contractions associated with accidental electrocution may produce vertebral fractures. This may account for the presence of bone marrow embolism in our 2 cases of electrocution, although the possibility of additional trauma following electric shock cannot be ruled out with certainty in either case. In the remaining 2 cases of bone marrow embolism without proved fractures there could be little doubt that fractures had actually occurred. One patient (case 10) died several minutes after a fall and pulmonary bone marrow embolism was extensive; in the other (case 17), careful inquiry among those in attendance prior to and at the time of death failed to disclose any history of trauma. Necropsy, however, revealed not only moderately severe bone marrow embolism but also extensive fat embolism in the pulmonary and systemic circulation. Moreover this patient was old, chronically ill, bedridden, and debilitated, conditions believed to contribute to the development of osteoporosis, which could account for the occurrence of fractures following relatively slight trauma.[30,31] Our observations thus substantiate Maximow's [3] original concept of the traumatic etiology of bone marrow embolism.

Associated fat embolism was found in 12 of 21 cases in which the material was suitable for the investigation of this feature. The diagnosis was always based upon the presence, within arteries or capillaries, of sudanophilic material morphologically acceptable as extracellular fat. In most instances in which pulmonary arterioles and capillaries were found to be occluded with minute fragments of bone marrow, it sometimes was difficult to determine with certainty, in sections stained for fat, whether intravascular fat globules represented intracellular or extracellular fat. It usually was possible, however, to recognize extracellular fat by the presence of droplets larger than fat cells or by their elongated, cast-like shape, particularly at the site of dividing vessels. Pulmonary fat embolism was considered to be severe in 3, moderately severe in 3, and mild to minimal in 6 cases. No direct relationship was observed between the severity of fat and bone marrow

embolism. In one of our 2 cases in which massive bone marrow embolism could be demonstrated by systematic examination of both lungs, fat embolism was minimal, and in the other it was absent.

An attempt was made to determine the physiologic and pathologic effects of bone marrow embolism. A survey of the clinical symptoms and signs which preceded death was unrevealing in most instances, particularly in those cases in which the severity of the shock, injuries to the brain or cervical spinal cord, or severe fat embolism made it impossible to attribute signs of respiratory distress to bone marrow embolism alone. Neither gross nor microscopic examination revealed pulmonary infarcts except in one case of congestive failure in which the lungs showed emboli secondary to mural thrombi of the heart in addition to bone marrow embolism. In some instances intra-alveolar hemorrhages were observed in the vicinity of bone marrow emboli. However, one could not be certain that they were actually caused by bone marrow embolism. Ceelen [32] stated that there were no sequelae of any consequence following bone marrow embolism and that even in embolization of small and medium-sized arteries an adequate collateral circulation was established promptly.

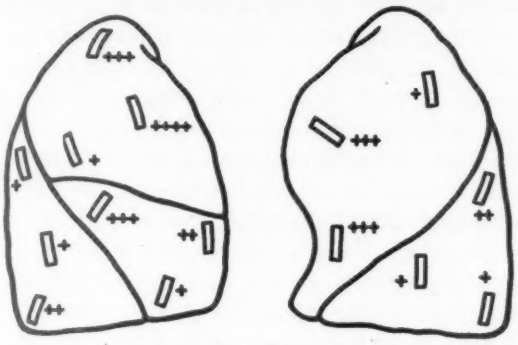
In most cases which we studied only a few vessels contained emboli. It is probable that in many of these cases, bone marrow embolism was an incidental finding and the pulmonary circulation was not signifi-



Text-figure 2. Case 10. Diagram showing distribution and severity of bone marrow embolism in sections taken from various areas of both lungs. Two-thirds of all sections taken contained bone marrow emboli. A.F.I.P. acc. 192095.

cantly impaired. In other cases, however, numerous intra-arterial fragments of bone marrow were observed and the extent and severity of the embolization could be demonstrated conclusively in 2 of them. Text-figures 2 and 3 are diagrams of the lungs in cases 10 and 26, respectively. Three sections from each lobe were taken in both

cases and the severity of bone marrow embolism in each section was graded. In case 10, 11 of 15 sections showed bone marrow embolism, although death followed the trauma almost immediately. No other changes to account for the patient's sudden death were found. This suggests the possibility that bone marrow embolism may on occasion



Text-figure 3. Case 26. Diagram showing distribution and severity of bone marrow embolism in the lungs. All sections taken showed bone marrow emboli. A.F.I.P. acc. 276915.

have the same lethal effect as other forms of pulmonary embolism. In case 26, that of a patient suffering from congestive heart failure who had generalized convulsions 2 days prior to death, every section showed bone marrow emboli. Although the post-mortem examination revealed other lesions to which the patient's death could be attributed, bone marrow embolism was so extensive and severe that it may well have been a contributory factor to the patient's death. In addition to these 2 cases in which both lungs were systematically examined for the purpose of determining the extent and severity of bone marrow embolism, there were 7 cases in which four or more sections were available and in which bone marrow embolism was found in more than one-half of the sections (cases 12, 15, 17, 18, 21, 25, 27). It is assumed that these cases, too, presented evidence of extensive and severe bone marrow embolism although this could not be proved conclusively on the basis of the material available for study.

To determine the incidence of bone marrow embolism in cases of traumatic death, 203 consecutive cases with multiple fractures were surveyed. Bone marrow embolism was found in 13 or 6 per cent. In addition it was observed in 1 of 35 cases of eclampsia, 3 of 15 cases in which death followed convulsive shock therapy for mental disorders, 1 of 5 cases of tetanus, and 2 of 34 cases of accidental electrocution. In a control series of 240 consecutive necropsies performed at a gen-

eral hospital in which cases of accidental death are infrequent, no instance of conclusively proved bone marrow embolism was found. In one case, however, a single intra-arterial fragment of fat tissue was observed which had some similarity to a bone marrow embolus but lacked identifiable myeloid cells (Fig. 16). At the periphery it was lined by endothelial cells, and lipid-laden macrophages were present between the fat cells. This structure was observed in a patient who died shortly after admission to the hospital for generalized abdominal pain. He had an old skull defect in the parietotemporal area as a result of combat duty, but denied having had epileptic seizures. Postmortem examination revealed acute generalized peritonitis due to a perforated gastric ulcer. On the information available it was not possible to explain to our satisfaction the presence of the intra-arterial tissue fragment. There was, however, some similarity between this embolus and the altered fat tissue in the vicinity of the perforated peptic ulcer, and the possibility of embolization of fat tissue at the time of perforation could not be completely rejected.

A point of interest is the shortness of the time interval (10 minutes or less) between injury or convulsion and death in 5 of our cases, including 2 in which extensive embolization seems to have occurred. This is in contrast to fat embolism in which massive embolization does not, as a rule, occur until several hours after the accident. It would indicate that a certain time must elapse before amounts of fat sufficiently large to produce extensive embolization are liberated from crushed fatty marrow or fat tissue, whereas bone marrow fragments apparently are detached and enter the circulation at the time of injury. There are also other differences between fat and bone marrow embolism. On the basis of our own observations and of the cases reported in the literature it can be considered almost certain that bone marrow embolism occurs only as a consequence of fracture, while fat embolism, although primarily a sequela of fracture, may also be encountered in its absence, *e.g.*, following blast injuries, pressure asphyxia, burns, carbon tetrachloride poisoning, and the introduction of oil into the organism for therapeutic purposes.[14] While fat embolism frequently occurs in the greater circulation, bone marrow embolism is found almost exclusively in vessels of the lung, the fragments being usually too large to pass through the pulmonary capillary bed. Only in one of our cases were occasional minute marrow fragments found in capillaries of the brain. A similar finding was reported by Karlén.[11] In neither case was an open foramen ovale observed.

The ultimate fate of the embolized bone marrow fragments has aroused some interest. Ogata[7] conducted experiments in which he in-

jected suspensions of bone marrow fragments from rabbits into other members of the same litter. He killed the animals at intervals of 1, 3, 5, 7, and 9 days, and observed that the bone marrow fragments underwent gradual disintegration. The cellular components of the red marrow were recognizable only until the third day, when pyknosis was apparent. The cells best preserved were the megakaryocytes. By the third day the vascular endothelium adjacent to the marrow fragments could no longer be distinguished; instead, fibroblasts extended into the marrow tissue. In rabbits killed after 5 days the marrow emboli were just barely recognizable as such and were amply penetrated by fibroblasts. After 7 days the greater part of the embolized bone marrow fragment was transformed into a calcified mass. Lengemann,[2] in similarly conducted experiments, found completely unchanged bone marrow fragments in animals killed after 3 days, while in those killed after 6 days the tissue fragments were hardly recognizable as bone marrow. In those killed after 10 days most of the emboli consisted of young vascular connective tissue in which occasional necrotic or calcified areas were visible. In those instances in which bone marrow embolism followed injection of emulsions of liver and kidney, Lubarsch[4] observed no change after 8 to 10 days in the rabbit, but found that a gradual disintegration occurred so that in the course of 4 weeks emboli were always resorbed or organized. To explain this difference in the survival of injected bone marrow emboli and those originating in the marrow of the examined animal, Lengemann[2] put forth the suggestion that tissue particles displaced from within the animal will be better preserved than those which are first removed from one animal and, after a variety of manipulations, injected into another.

Lubarsch[4] stated that in one of his cases of eclampsia he observed an essentially unaltered bone marrow particle 5 days after the presumptive occurrence of the embolization. In none of the traumatic cases of our series were degenerative changes observed in the fat or myeloid cells, but early necrosis of fat cells was seen in one of the non-traumatic cases (case 26). Definite changes were seen also in the 3 cases of convulsive shock therapy. These included endothelialization of those portions of the surface of the embolus which were not adherent to the vascular wall, fibroblastic proliferation into the marginal portions of the embolus, diminution of easily recognizable myeloid and erythroid elements, and a scattering of fat-laden macrophages (Fig. 13). Due to the fact that these patients had had several "shock" treatments prior to death, the time at which embolization occurred could not be determined with any degree of accuracy.

The material presented indicates that bone marrow embolism,

although not common, occurs more frequently than is generally realized. In several instances it was the only available evidence of fracture; in such cases the finding of bone marrow emboli may aid in the clarification of the circumstances of an otherwise unexplained death and thus be of medicolegal significance. Our observation of massive pulmonary bone marrow embolism, established in 2 cases by systematic examination of both lungs and considered probable in 7 additional cases because of numerous emboli in the sections available, suggests that bone marrow embolism may, on occasion, be a primary or a contributory cause of death.

Summary

The clinical data and histologic observations in 27 cases of pulmonary bone marrow embolism indicate that embolization of marrow fragments occurs as a consequence of fracture-producing trauma to red marrow-containing bone. These fractures need not always be the result of external injury, but may be due to sudden violent muscular contractions as they occur in convulsions from any cause.

The displacement of bone marrow fragments into the venous circulation following fracture may well be explained by the anatomical structure of cancellous bone in which the marrow is separated by only a single layer of endothelial cells from the lumina of the intramedullary sinusoidal blood spaces. The increased local pressure produced by hemorrhage and edema incident to fracture may force marrow fragments into veins by way of the disrupted sinusoids.

In a survey of more than 200 cases of accidental death with fractures, pulmonary bone marrow embolism was found in 13, or 6 per cent.

The extent and severity of bone marrow embolism varied considerably; in some instances it was found only in an occasional section from the lung. In others, however, embolization was so extensive that it may well have produced significant impairment of the pulmonary circulation.

Bone marrow embolism may or may not be associated with fat embolism. There was no direct correlation between the severity of fat embolism and that of bone marrow embolism in the series of cases reported.

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DESCRIPTION OF PLATES

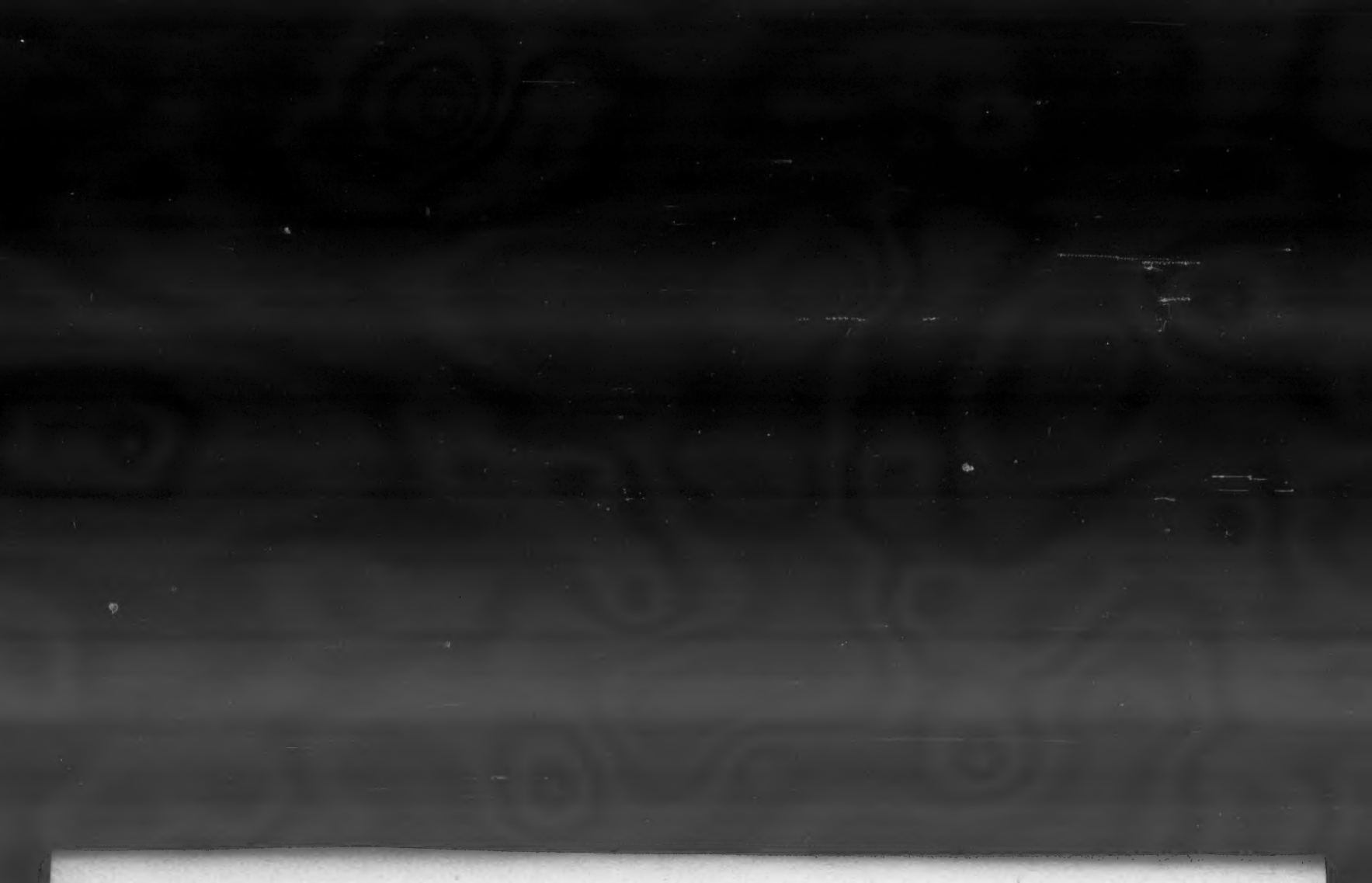
PLATE 77

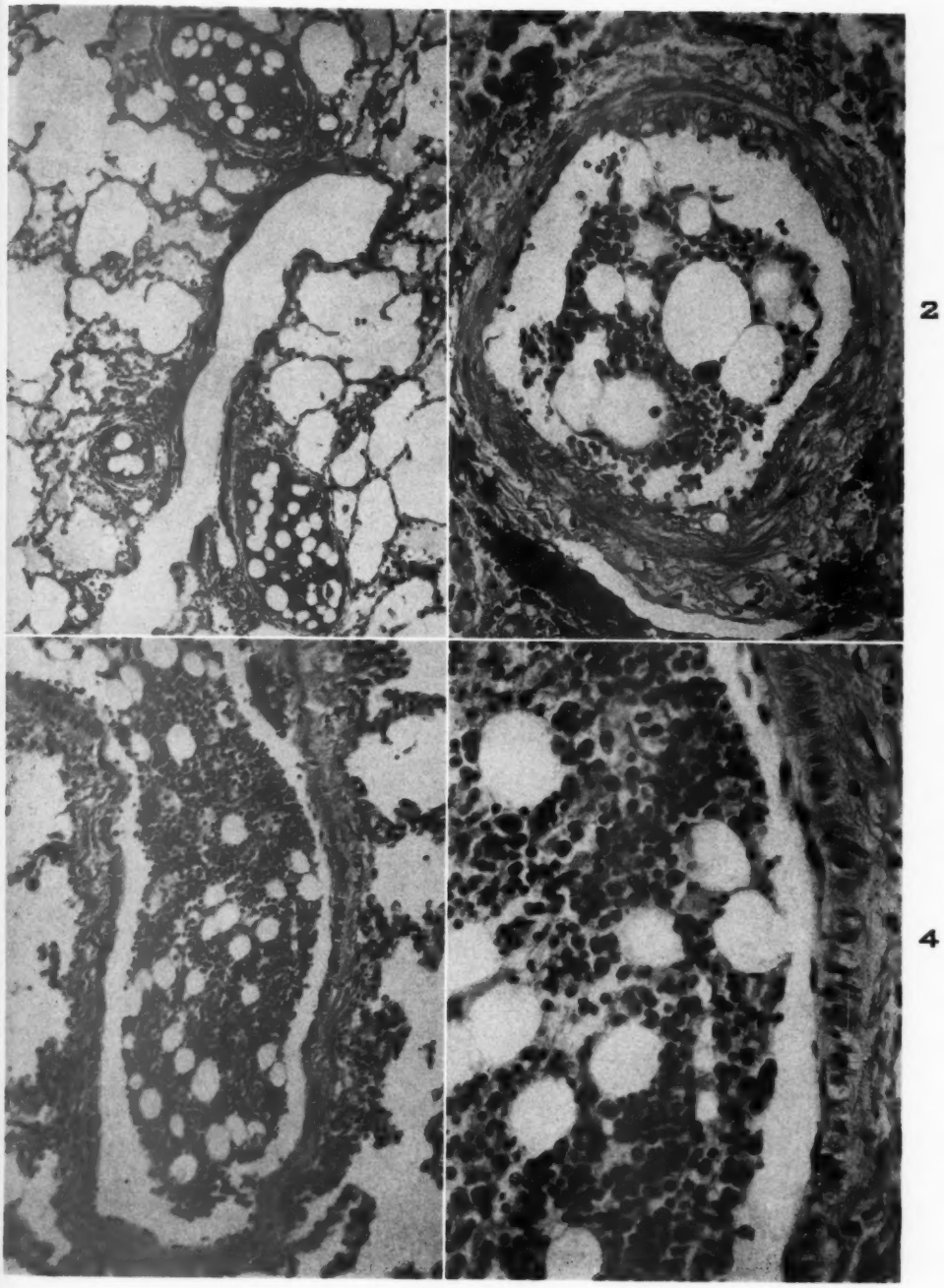
FIG. 1. Case 18. Multiple pulmonary bone marrow emboli. Armed Forces Institute of Pathology accession no. 281817. × 55.

FIG. 2. Case 26. Cross section of a bone marrow embolus in a medium-sized pulmonary artery. A.F.I.P. acc. 276915. Veterans Administration Hospital negative no. 573A. × 200.

FIG. 3. Case 10. Bone marrow embolus in a medium-sized pulmonary artery. Longitudinal section. A.F.I.P. acc. 192095. × 100.

FIG. 4. A portion of Figure 3 at a higher magnification, showing myelocytes, foci of erythroblasts, and one megakaryocyte. × 375.





Rappaport, Raum, and Horrell Bone Marrow Embolism

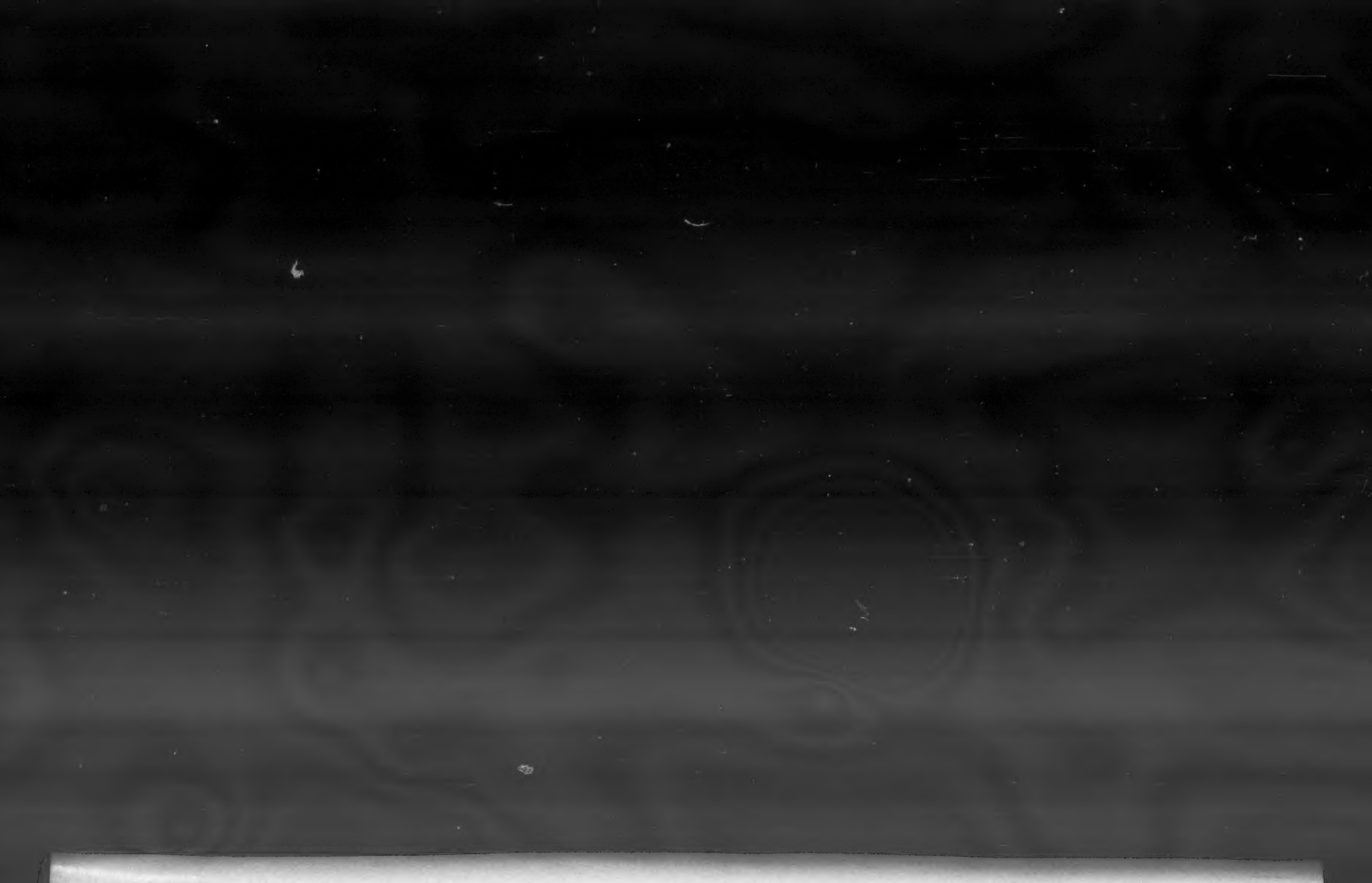
PLATE 78

FIG. 5. Case 26. Bone marrow embolus with bone spicules. A.F.I.P. acc. 276915. V.A.H. neg. 573B. × 220.

FIG. 6. Case 26. Small intravascular bone fragments almost completely devoid of marrow elements. A.F.I.P. acc. 276915. V.A.H. neg. 573C. × 300.

FIG. 7. Case 26. Bone marrow embolus at site of bifurcation of artery which appears to be distended. A.F.I.P. acc. 276915. V.A.H. neg. 573D. × 125.

FIG. 8. Case 26. Bone marrow embolus in a medium-sized pulmonary artery. The portion of the lumen not occupied by the embolus shows recent thrombosis. A.F.I.P. acc. 276915. V.A.H. neg. 573E. × 100.



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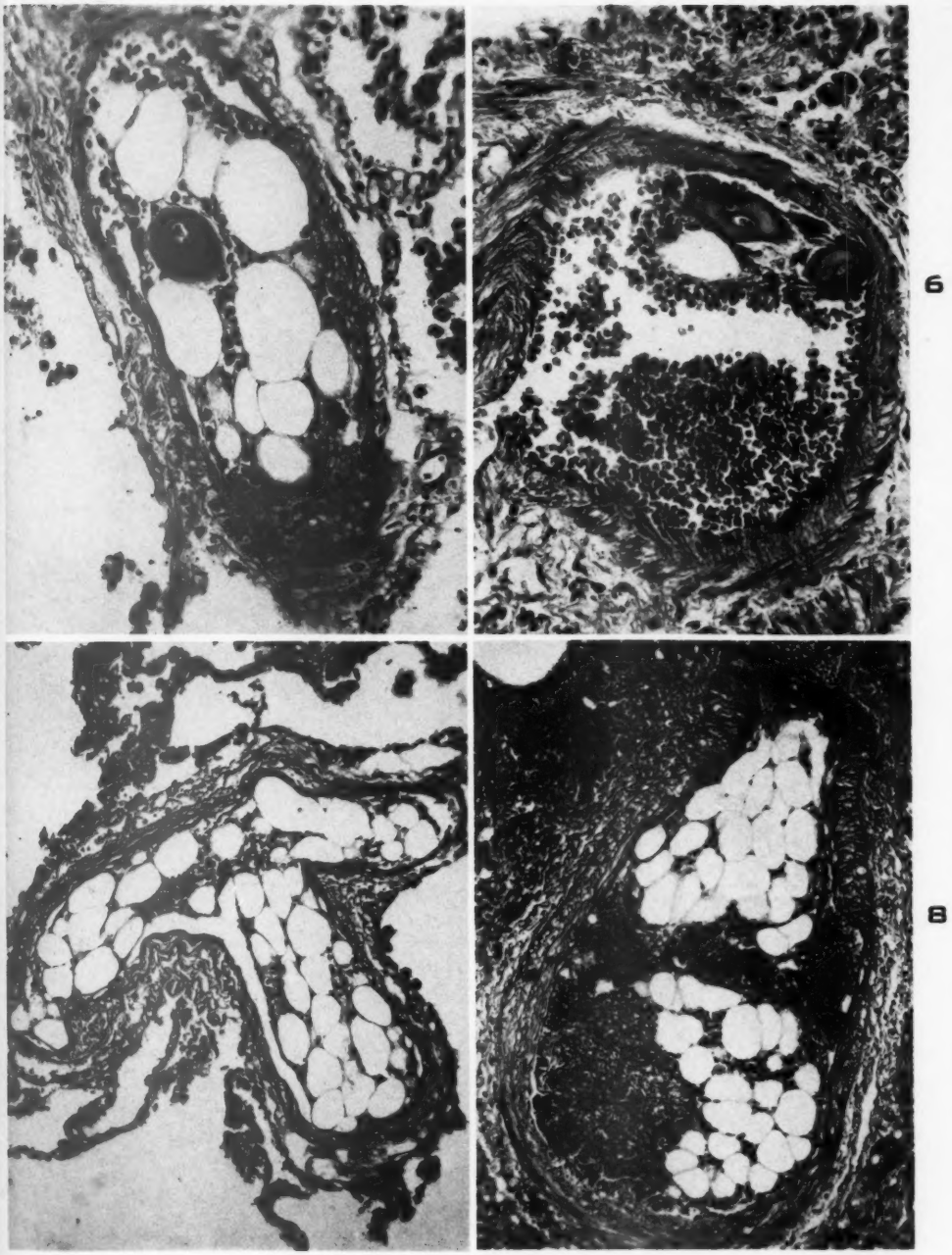

Rappaport, Raum, and Horrell Bone Marrow Embolism

PLATE 79

FIG. 9. Case 10. Portion of a bone marrow embolus containing a group of arterioles. A.F.I.P. acc. 192095. V.A.H. neg. 376. × 300.

FIG. 10. Case 26. Small bone marrow emboli consisting almost entirely of fat cells, within pulmonary arterioles. In frozen sections stained for fat these emboli may be indistinguishable from fat embolism. A.F.I.P. acc. 276915. × 275.

FIG. 11. Case 18. Small bone marrow embolus in an interalveolar capillary. A.F.I.P. acc. 281817. × 600.

FIG. 12. Case 17. Small bone marrow embolus in a cerebral capillary. A.F.I.P. acc. 269555. × 600.

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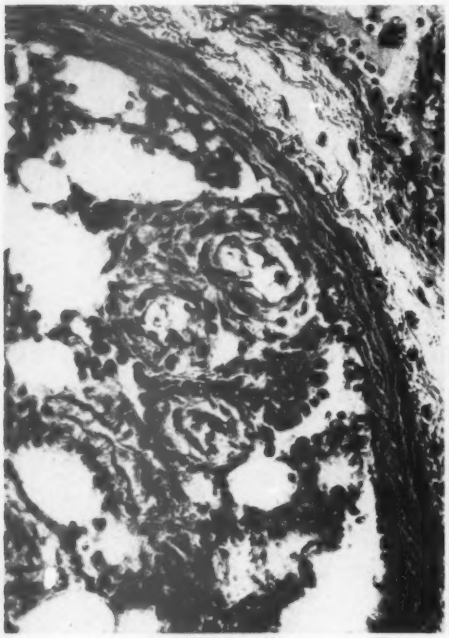

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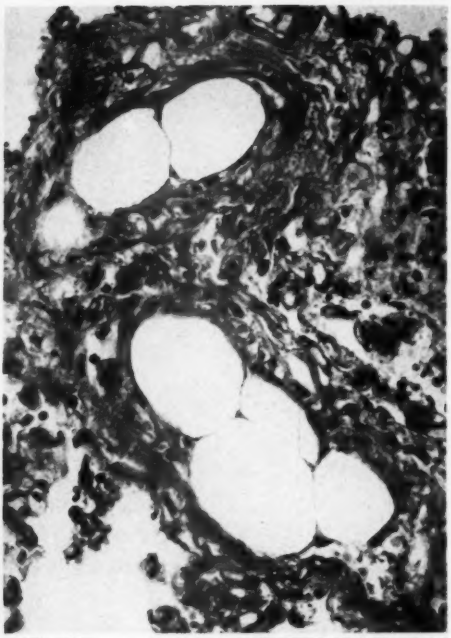

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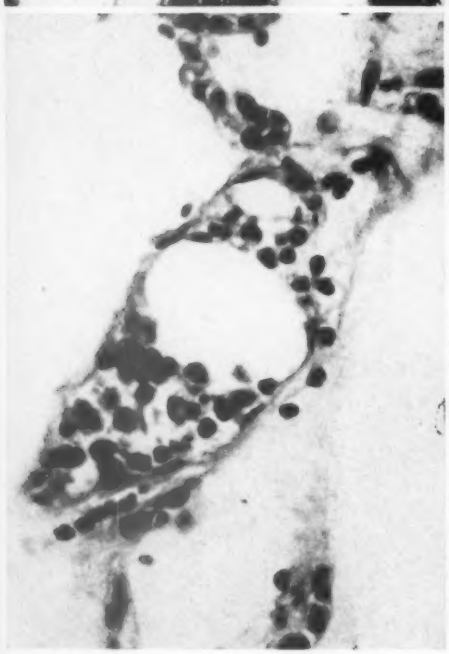

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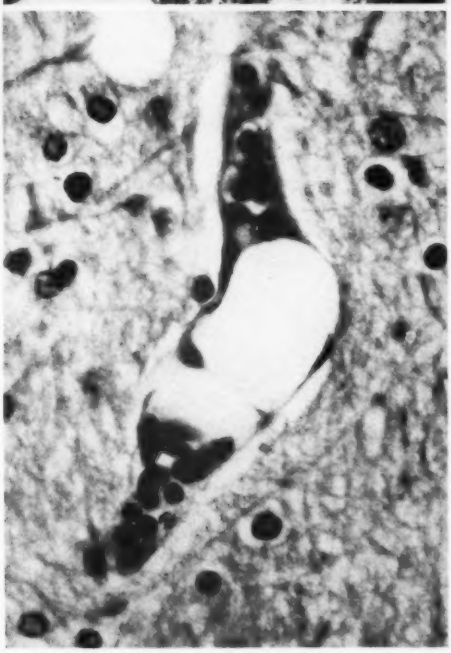

12

Rappaport, Raum, and Horrell Bone Marrow Embolism

Plate 80

Fig. 13. Case 24. A somewhat older bone marrow embolus in a medium-sized pulmonary artery. The free margin is covered with endothelium. There is subendothelial fibroblastic proliferation. Scattered lipid-laden histiocytes are seen. A.F.I.P. acc. 159159. × 165.

Fig. 14. Case 1. Bone marrow embolus entrapped within a recess between pectinate muscles of the right auricle. A.F.I.P. acc. 72964. × 80.

Fig. 15. Case 27. Bone marrow embolus. Sudan III stain. A.F.I.P. acc. 276108. × 275.

Fig. 16. Intravascular structure resembling a bone marrow embolus (an incidental finding in a section of lung from one of the cases of the control group); no myeloid elements identified. The exact origin of this material could not be determined. A.F.I.P. acc. 230244. × 275.

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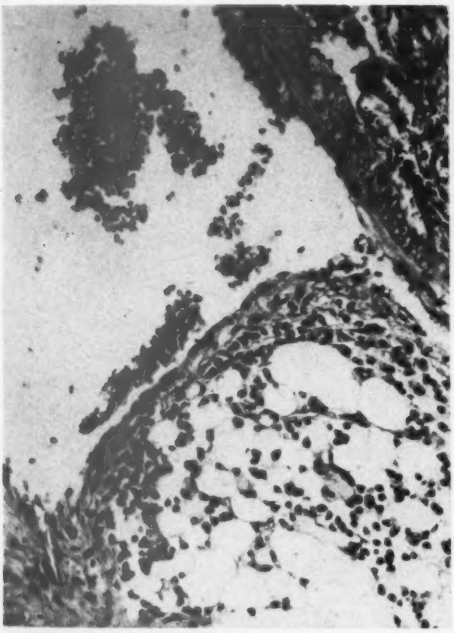

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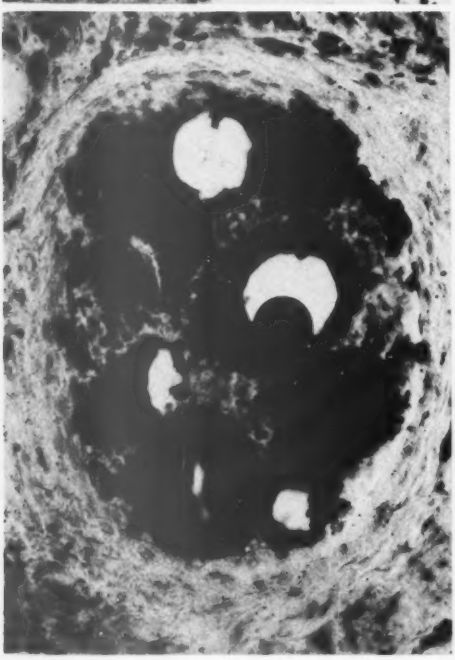

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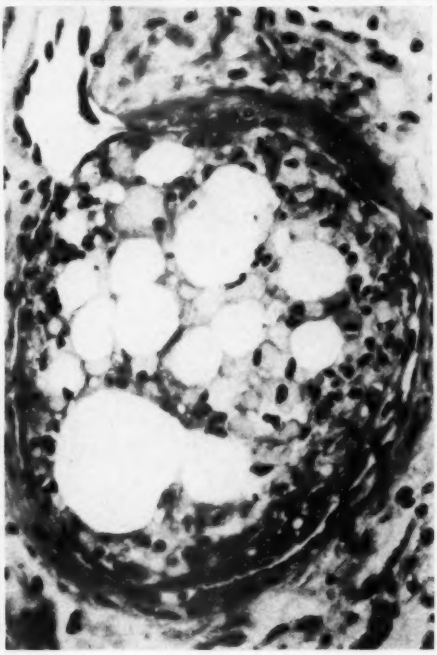

16

Rappaport, Raum, and Horrell Bone Marrow Embolism

THROMBOSIS OF THE RENAL VEINS WITH MASSIVE HEMORRHAGIC INFARCTION OF THE KIDNEYS IN CHILDHOOD

Report of Four Cases *

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Hemorrhagic infarction of the kidneys secondary to venous thrombosis is a relatively uncommon condition. This is evidenced by the fact that we have found only 4 cases among 1,092 necropsies performed at the Children's Memorial Hospital during the past 12 years, constituting an incidence of 0.37 per cent. This is in accord with the recent report of Fallon.[1] Although the German literature is said to demonstrate a higher incidence,[2-4] Abeshouse,[5] in a review of the literature on this subject in 1945, was able to collect a total of only 228 cases. Since that time 7 cases have been reported [1,3,6] which, with our 4 cases, bring the total number to 239. In terms of the total number of necropsies performed, Abeshouse stated, the incidence varied from 0.027 to 2.0 per cent. Most of the figures place the incidence at lower than 1.0 per cent.

Interest has been manifested recently in hemorrhagic renal infarction because of the reports of successful surgical removal of one kidney in 2 cases by Campbell and Matthews [7] and in one case by Sandblom.[6] The correct diagnosis was made preoperatively in only one case.[7] Previously the diagnosis had been made after surgical removal of a kidney on the basis of an incorrect original diagnosis.[2]

It is believed that a report of 4 additional cases is justifiable on the basis of the relative rarity of the lesion, and because these cases illustrate a sequence of events in the pathogenesis of hemorrhagic renal infarction which appears to be of some importance in children suffering from non-renal infections accompanied by dehydration resulting from diarrhea and vomiting.

Report of Cases

CASE 1

A white female child, 3 weeks old, was admitted to the Children's Memorial Hospital on November 17, 1947, with a history of five to six very loose, greenish stools daily, and the refusal of fluids for 10 days prior to admission. From November 8 to 10 the diarrhea had ceased, but recurred and persisted for the 5 days prior to admission. Blood was said to have been mixed with the stools, and the child was feverish. The family history was not contributory.

* Received for publication, June 19, 1950.

Physical examination on admission revealed a well developed and well nourished infant. She was slightly hypertonic and held her head in extension, but the Brudzinski and Kernig signs were negative. There was a sweetish odor to the breath, respirations were rapid and deep, and she appeared acidotic. No masses were felt in the abdomen, and physical examination was otherwise negative. The hemoglobin was 10.3 gm. per 100 cc.; white blood cells, 10,600 per cmm.; differential count showed neutrophils, 5,250; lymphocytes, 4,515; monocytes, 210; staff cells, 525 per mm. The clinical impression was diarrhea and vomiting associated with starvation ketosis (dysentery?).

The child was febrile throughout the course of the disease. Dehydration was combatted with moderate success by vigorous intravenous fluid therapy with plasma, amigen solution, and glucose-saline solution. Five to six liquid stools were passed each hospital day. On the second day she appeared comfortable and hydration was adequate. At that time two masses were palpated in the abdomen, which were considered to be enlarged kidneys. The urine appeared grossly bloody, contained 100 to 200 mg. of albumin per 100 cc., and microscopic examination of the centrifuged specimen revealed very few red blood cells. However, the orthotoluidine test for hemoglobin was moderately to markedly positive in successive specimens. On the fourth day, the non-protein nitrogen was 95 mg. per 100 cc. The masses were still present in the abdomen and the liver was palpable 1 cm. below the costal margin. The child expired early in the morning of the sixth hospital day.

Clinical Diagnosis. Bilateral polycystic kidneys.

Post-mortem Examination

At necropsy (A 47-128) the body was poorly nourished, but normally developed, measuring 51 cm. in length and weighing 2,950 gm. No external abnormalities were noted.

The lungs together weighed 70 gm. (normal, 55 gm.) and showed slight dependent congestion. A yellowish thrombus occluded the pulmonary artery to the left lower lobe. The liver weighed 195 gm. (normal, 127 gm.), but showed no gross lesions. The gastro-intestinal tract showed no evidence of ulceration. Each middle ear contained a small amount of mucopurulent material.

Both kidneys were markedly enlarged, the right weighing 26 gm., and the left, 30 gm. (normal, 15 gm. each). Externally, the left kidney exhibited a mottled hemorrhagic discoloration both before and after the capsule was removed. The capsule stripped easily and the underlying surface was smooth. On section, the cut surfaces (Fig. 2) were markedly abnormal and showed broad, bulging, hemorrhagic zones occupying the whole medulla and inner half to two-thirds of the cortex. The remaining cortex was relatively normal with occasional hemorrhagic streaks extending out to the surface and corresponding to the hemorrhagic areas seen on the surface. The pyramids were involved in such a way as to leave a relatively free zone of cortical tissue penetrating deeply between them so that they were clearly demarcated from one another. The normal medullary striations were completely obliterated. The left main renal vein (Fig. 2) was occluded

by a brownish yellow thrombus which was firmly adherent to the wall and could be seen extending into the larger branches. It pouted into the inferior vena cava which was not thrombosed. Externally, the right kidney showed no discoloration, but on section (Fig. 1) there was a patchy hemorrhagic discoloration in the inner zone of the cortex and outer layers of the pyramids, accurately outlining the latter. The right main renal vein (Fig. 1) was incompletely occluded by a yellowish white thrombus which was not so firmly adherent to the wall as that on the left. Both renal arteries were empty. The urinary pelves and ureters were not unusual.

Microscopic Examination

Microscopic examination of the *lungs* revealed scattered areas of peripheral atelectasis in the lower lobes, some hyperemia of the alveolar walls, with intra-alveolar hemorrhage in the upper lobes. A large branch of the pulmonary artery to the left lower lobe was occluded by a thrombus undergoing organization and partly covered by endothelium. Acute inflammatory exudate was present in the middle ear.

The medulla of the *left kidney* (Fig. 4) was completely replaced by red blood cells with only the faintest trace of normal architecture still present. The inner portion of the cortex was similarly involved. In the peripheral portion of the cortex the tubules were intact but compressed by the hemorrhage in the interstitial tissue. Many of these contained hyaline casts and a few red cells and pigment, resembling hematin and hematin casts. The glomeruli were not unusual. Several large veins of arcuate and interlobular size contained thrombi in which organization was proceeding and was quite advanced in some (Fig. 4). The main renal vein in its intrarenal course also contained a thrombus in which organization was less advanced than in the arcuate veins. In the distal, free portion of the main vein (Fig. 5) there was no detectable organization of the thrombus. The thrombi were, then, oldest in the arcuate veins and most recent in the free portion of the renal vein. No inflammatory reaction was present in the vein walls or in the surrounding tissues.

The *right kidney* showed patchy dilatation and engorgement of capillaries in the areas of discoloration grossly. There was little actual hemorrhage and the tubules were, for the most part, compressed, but not destroyed in these areas. The glomeruli were not unusual. The tubules contained granular, hyaline, and a few hematin-like casts. Several large arcuate veins contained organizing, non-occlusive thrombi in which the organization was not as advanced as in the corresponding vessels in the left kidney. The main renal vein also contained a

thrombus which was homogeneous and granular with no organization. No inflammatory exudate was present anywhere in the kidney, vessels, or capsule.

Anatomical Diagnosis. Bilateral otitis media; bilateral thrombosis of renal veins with complete hemorrhagic infarction of left kidney and focal infarction of the right kidney. Organizing thrombi of main and smaller branches of left pulmonary artery.

CASE 2

A female child, 14 months old, was admitted to the Children's Memorial Hospital on November 30, 1936. In the latter part of September it was first noticed that the child was developing pallor and lack of appetite, which became gradually worse. During the third week of November she became irritable. Examination of the urine at this time revealed considerable pus. Following this, "stringy" red material was seen in the urine and she began to vomit. Bright red blood had been observed in the stools on one occasion in August, and for the 2 months prior to admission she had been constipated. Physical examination 2 days prior to admission revealed no abdominal masses, and the clinical diagnosis was nutritional anemia and pyuria. The previous history was negative except for an attack of diarrhea at the age of 10 months.

Physical examination on admission showed a waxy, pale, poorly nourished child with a temperature of 101.4° F. In the left side of the abdomen there was a very hard mass, extending from the costal margin to the anterior superior spine. The right kidney extended to the level of the umbilicus. Palpation of the mass by rectum was not possible. The hymen was imperforate and the remainder of the examination was negative. The impression was that the mass on the left side was retroperitoneal, probably a tumor of the kidney or adrenal gland.

The urine of December 1 and 2 contained 300 pus cells per high-power field in centrifuged specimens, but no albumin, glucose, acetone, or diacetic acid was detected by chemical tests. Culture showed a moderate growth of *Bacillus acidi lactici.* Examination of the blood revealed red blood cells, 1.5 millions; white blood cells, 43,000; hemoglobin, 19 per cent; differential: neutrophils, 80 per cent; lymphocytes, 13 per cent; monocytes, 5 per cent. Chemical determinations of the blood were: urea nitrogen, 94 mg. per 100 cc.; uric acid, 7.2 mg. per cent; urea, 201 mg. per cent; creatinine, 3.09 mg. per cent. Wassermann test of the blood was negative and stool culture grew no pathogens.

Transfusions were given on admission, with temporary increase of the hemoglobin to 28 per cent. On December 3, a second abdominal mass, which was firm, somewhat tender, and ballotable, was palpated in the right loin. An intravenous pyelogram was attempted but was unsuccessful. A flat plate of the abdomen revealed a mass in the region of the right kidney. A few stringy blood clots were present in the urine. On December 3, the patient became anuric and remained so until death. Intravenous fluids were administered, but by December 7 the abdominal masses had increased in size; edema of both legs and ascites were present by December 13, and she died on December 14. This was at least 2 months after the appearance of urinary symptoms and 14 days after abdominal masses were noted.

Clinical Diagnosis. Uremia, cause undetermined.

Post-mortem Examination

At necropsy (A 36–88) the body was that of a poorly nourished but well developed, pale, white female child whose body length was

75 cm. The peritoneal cavity contained about 150 cc. of clear, straw-colored fluid. There was some distention of the ileum, and of the ascending and transverse colon. The descending colon and splenic flexure were adherent to the left kidney and the ascending and hepatic flexures to the right; otherwise the gastro-intestinal tract was normal. The mesenteric lymph nodes were enlarged to almost twice normal size. The remaining organs, other than the kidneys, were grossly normal.

The right kidney weighed 128 gm. (normal, 36 gm.). Externally, the surface was whitish with marked injection and reddening of the surrounding connective tissue. On the cut surface, the capsule appeared thickened and white, measuring approximately 0.1 cm. in width with a very narrow band of normal-appearing kidney substance attached. Beneath this was a narrow yellowish white zone. Cleavage between the capsule and the outer kidney substance occurred easily. The remaining kidney tissue showed a dark red, hemorrhagic, moist surface, almost gelatinous in appearance. The cut surface bulged slightly. Normal markings were indistinct.

The left kidney weighed 188 gm. (normal, 35 gm.). Fibrous tags were present on the external surface of the capsule, where it had been adherent to the colon. The appearance of this kidney was similar to that of the right except that there was complete obliteration of the normal markings, and there were soft, yellowish, necrotic areas with early cavitation present. The cut surface did not bulge as much, nor did as much fluid blood exude from the surface. The wall of the urinary bladder was thickened, the mucosa was reddened, and the lumen contained a very small amount of blood-stained urine. The lumen of the inferior vena cava was occluded by a thrombus which was white above and red below the origin of the right renal vein, extending slightly more than 2.0 cm. above and below this point. Both renal veins were occluded by thrombi which were white and firm on the left and red and soft on the right. The thrombi could be seen, grossly, to extend well into the hila. The adrenals were adherent to the capsules of the kidneys by firm fibrous adhesions. They were darker yellow and somewhat softer than normal. The right weighed 2.4 gm. and the left, 3.1 gm.

Microscopic Examination

Microscopically, both *kidneys* had a similar appearance. The whole medulla, in most of the sections, except for the formation of abscess-like cavities at the tips of the pyramids, was represented by a necrotic shadow of its former structure, obscured by the presence of degen-

erated and laked red blood cells. Many of the tubules contained remnants of neutrophilic leukocytes and red cell débris. Within the necrotic areas, the ghosts of veins of all sizes containing fairly recent thrombi were present. The inner two-thirds of the cortex and patches extending out to the capsule were involved in a similar process. The outer third of the cortex appeared free from hemorrhage, but the tubules, glomeruli, and vessels were necrotic, with a marked neutrophilic exudate and ingrowth of fibroblasts and capillaries from the capsule. No significant bacteria could be demonstrated in the sections. In a few areas near the hilum of the kidney the tissue of the cortex was better preserved, and there the tubules were filled with polymorphonuclear leukocytes and red cell débris. The capsule was markedly thickened by collagenous tissue older than the granulation tissue in the cortex. This organization was more advanced on the left than on the right. The peripelvic fat showed a marked inflammatory reaction with early granulation tissue formation.

The large intrarenal branches of the *renal vein* and some smaller arcuate veins in the medulla were thrombosed. The cellular elements of the thrombi in the main renal veins were better preserved on the right where organization was not present. On the left, the red cells in the thrombus were laked and considerable organization had occurred. The thrombus in the inferior vena cava appeared intermediate in age between the thrombi of the two renal veins as judged by hyalinization and organization. The inflammatory reaction of the peripelvic tissue approached only the outer layers of the adventitia of the veins. Otherwise the veins were free of exudate. One artery showed a non-occlusive thrombus associated with the marked peripelvic inflammatory reaction. A small segment of the artery was necrotic. However, bacteria were not demonstrable in the neighborhood and the thrombus was much more recent than those in the veins.

The *urinary bladder* showed thickening of the wall by edema and a moderate lymphocytic infiltration of the submucosa. In one ureter there was a moderate chronic inflammatory reaction, comparable to that in the bladder. The lungs showed mild interstitial pneumonitis and marked peribronchitis. Numerous large pulmonary veins and arteries contained thrombi, some showing advanced and others slight organization. The central vein of the left adrenal gland contained a very recent thrombus, but there was no lesion of the parenchyma. A pure culture of hemolytic streptococci was obtained from the heart's blood.

Anatomical Diagnosis. Bilateral non-inflammatory thrombosis of

the renal veins and inferior vena cava with bilateral hemorrhagic infarction of the kidneys; minimal pyelonephritis with low grade ureteritis and cystitis; recent thrombosis of left adrenal vein; thrombosis of pulmonary veins and arteries; mild interstitial pneumonitis and peribronchitis; hemolytic streptococcal septicemia (post-mortem culture).

CASE 3

A white female child, 2 months old, was admitted to the Medical Service of the Children's Memorial Hospital on November 13, 1935, with a history of diarrhea and vomiting of 2 days' duration; of profuse nasal discharge for 4 days; and of collapse, cyanosis, and dehydration the day before admission. The child had been in the Foundling Division since birth, under observation for possible congenital syphilis. However, no evidence of congenital syphilis was found after intensive investigation.

On admission the physical examination revealed a reddened throat and evidence of dehydration. Temperature was 99.0° F. Blood count on November 17 showed red blood cells, 3.6 millions; white blood cells, 22,300; hemoglobin, 70 per cent; differential count: polymorphonuclear leukocytes, 50 per cent; lymphocytes, 36 per cent; eosinophils, 0; monocytes, 3 per cent; degenerated cells, 11 per cent. Transfusions were given. From November 13 to 18, the rectal temperature varied from 99° to 102° F. By November 18 vomiting and diarrhea had decreased somewhat, but on November 20 there was an exacerbation of the symptoms with the addition of a severe cough. Bronchial breathing and impaired resonance were found over the right lower lobe, and roentgenograms demonstrated consolidation of most of the right lung. The fever became more marked, with temperatures varying from 100° to 104° F. On November 22 the temperature reached 105° F., and was 106° F. on November 23. The patient was cyanotic, her respirations were rapid, and there was a loss of 1½ lbs. in weight. Death occurred on the eighth hospital day. There was no record of a urinalysis.

Clinical Diagnosis. Acute lobar pneumonia with diarrhea.

Post-mortem Examination

At necropsy (A 35–90) the body was that of a fairly well nourished white female infant, 53 cm. long.

There was extensive consolidation of both lungs with minute abscesses near the apices on both sides. The process involved more than three-quarters of the functioning lung parenchyma, the upper lobe more than the lower on the right, and the reverse on the left. There was considerable thick fibrinous exudate in the interlobar fissure between the right middle and upper lobes. The bronchial and hilar lymph nodes were not remarkable.

The left kidney and renal vessels were not unusual in any way, the kidney weighing 12.3 gm. (normal, 15 gm.). The right kidney weighed 19.5 gm., was grossly enlarged, and the external surface was mottled by large, dark red patches, most evident at the lower pole. The right renal vein, as it entered the hilus, was blocked completely by a yellowish white thrombus, which extended into many of the

smaller branches. Serial cross sections of the organ revealed the pyramids to be dark red with a few streaks of yellow. The cortex was indistinct and at one pole there was a tiny yellowish triangular area.

Microscopic Examination

Microscopically, the *lungs* showed an extensive bilateral bronchopneumonia with abscess formation and patchy interstitial and lipoid pneumonia. There were non-occlusive recent thrombi in several small pulmonary arteries and veins.

The *right kidney* showed extensive thrombosis of the renal veins. The venae recti and arcuate veins contained thrombi which were undergoing moderate organization (Fig. 6), whereas the thrombus in the main renal vein showed no organization (Fig. 7). The medulla, inner portions, and patches of the outer portion of the cortex showed, in addition to venous thrombosis, marked engorgement of all of the venous and capillary channels, with hemorrhage into, and necrosis of, the tubules. The glomeruli were engorged but gave no evidence of necrosis. Many cortical tubules contained casts, red cells, red cell débris, and occasional white blood cells. Inflammatory reaction was present at the tips of the pyramids where tiny areas of early abscess formation could be seen. Bacteria could not be stained in significant numbers, and these abscesses appeared to be localized areas of severe aseptic necrosis. The pelvis and peripelvic tissues were normal.

The *left kidney* showed no microscopic lesions.

Cultures of the heart's blood and lung abscesses grew beta hemolytic streptococci and *Staphylococcus pyogenes*.

Anatomical Diagnosis. Bilateral bronchopneumonia with abscess formation; septicemia; recent thrombosis of right renal veins and of small pulmonary veins and arteries; focal hemorrhagic infarction of right kidney.

CASE 4

A male infant, 1 month of age, was admitted to the Medical Service of the Children's Memorial Hospital on July 22, 1937. He had been perfectly well until 24 hours prior to admission, when he began to vomit. On the day of admission he had five liquid, green stools. The child weighed 7½ lbs. at birth and the family and previous histories were non-contributory.

Physical examination on admission was fragmentary, due to the grave condition of the child. He was markedly dehydrated with very dry, loose, and inelastic skin, and with a sunken fontanelle. There was an ashen gray pallor. The breath smelled strongly of acetone. Temperature was 99° F. No urinalysis was recorded.

Intravenous therapy was attempted through the right ankle but failed and was then instituted through an incision in the left ankle. Fluids were administered subcutaneously also, and the dehydration was somewhat alleviated. Shortly afterwards the right foot became cold and blue. The temperature rose to 102° F. and he passed several liquid stools. The day after admission, the right foot was very blue, particu-

larly in the region of the third toe. Several liquid, bloody stools were passed and vomiting of coffee-ground material occurred. A blood transfusion was begun but the child died after only 20 cc. had been given.

Clinical Diagnosis. Acute intestinal intoxication with severe dehydration and acidosis.

Post-mortem Examination

At necropsy (A 37–56), the body was that of a poorly nourished, male child. The body length was 51 cm. There was marked cyanosis of the face, lips, and fingernail beds. The distal half of the right foot was edematous and deep bluish red. There were fresh incisions over both medial malleoli.

The lungs weighed 46 gm. each (normal, 31 gm.). The right was deeply congested but crepitant. The cut surface was bloody and mottled with deep red areas. The bronchi were deeply reddened and covered with thin mucoid secretion. The left lung was deep pink to red. The lower lobe was firm and deep red, while the upper was subcrepitant. On section, the cut surface of the lower lobe was bloody and liver-like in appearance and consistency. The upper lobe was congested.

The left kidney weighed 19.8 gm. (normal, 15 gm.). It appeared normal in size and shape. On section the markings were distinct and not altered in any way.

The right kidney weighed 24.2 gm. It was slightly larger than the left, and dark red on its external surface. The main renal vein was occluded by a red thrombus, which was easily dislodged. On section of the kidney the large branches of the vein were seen to be occluded by similar material. The medulla and parts of the cortex between the pyramids were dark red with flecks of yellow, and gelatinous, with obliteration of the normal markings. The peripheral third of the cortex appeared uninvolved.

The right saphenous vein, distal to the point of ligature at the medial malleolus, was filled with red clot, extending throughout the venous plexus to the toes. On the left side there was only a small thrombus in the immediate vicinity of the ligature.

The remainder of the organs were normal.

Microscopic Examination

There was extensive focal pneumonia in the right lower lobe of the *lungs*. The other lobes showed congestion and a minimal degree of interstitial pneumonia. A few venules contained hyaline thrombi. Sections of the right saphenous vein showed a thrombus surrounded by more recent clot.

In the *right kidney* there had been extensive hemorrhage into the interstitial tissues. This largely obliterated the pyramids and there was extensive necrosis of the tubules in these areas. In the cortex, the venules and arcuate veins were occluded by hyaline and fibrinous thrombi showing no evidence of organization and containing red cells in a relatively good state of preservation (Fig. 3). The main renal vein and its principal branches also were occluded by a recent thrombus without organization. There was no evidence of inflammation of the vessel walls or of the surrounding tissues. There was streaky interstitial hemorrhage in the inner two-thirds of the cortex. Coagulative necrosis of the convoluted tubules was present in this region (Fig. 3), and extended only into the outer third in small patches. However, for the most part, the outer third of the cortex was normal. Many of the glomeruli were markedly congested. Some hemorrhage was present in the tissues surrounding the renal pelvis.

Anatomical Diagnosis. Alveolar pneumonia of the lower lobe of the right lung; thrombosis of the right renal veins with hemorrhagic infarction of the right kidney; thrombosis of the saphenous vein of the right foot with early gangrene; thrombosis of venules of the lung.

Discussion

Clinical Aspects

Clinical and laboratory observations were few in these cases because of the short duration of life after admission to the hospital and the extremely grave state of the patients.

The most prominent presenting symptom complex was diarrhea and vomiting. Attention was directed toward the urinary tract from the history in only one case, in which pyuria and hematuria had been noted for some time prior to the onset of the terminal illness. Pneumonia was detected in one case (case 3). Abdominal masses were noted in only 2 of the 4 cases during life (cases 1 and 2) and were correctly considered to be kidneys. Urinalysis showed hemoglobinuria and albuminuria in case 1 and pyuria in case 2. In the same cases, the non-protein nitrogen was markedly elevated. Urinalysis was not done in the other cases. Anemia was present in 3 of the 4 cases. The patients did not present any common pattern of clinical course other than that of marked pyrexia and diarrhea with or without vomiting, which resulted in dehydration. The correct diagnosis was not made ante mortem in any case.

Clinical observations indicate that the appearance of abdominal masses in children having the signs of sepsis with or without diarrhea

should suggest the possibility of renal infarction, particularly when associated with such findings as albuminuria, hemoglobinuria, hematuria, or pyuria, singly or in combination. Some regard hemoglobinuria as the most specific sign,[3] but as judged from our cases and those in the literature, this does not occur with great regularity. Indeed, in the series reported by Barenberg, Greenstein, Levy, and Rosenbluth [8] few abnormal urinary findings were noted. There was a trace of albumin in 3 of the 5 cases, an occasional red blood cell in the sediment of 3, and all had an occasional white blood cell. These emphasize the possible importance of apparently negligible findings.

In reviewing the German literature, Hepler [2] found that the most common syndrome was a sudden onset of hematuria, lumbar pain, and enlargement of the kidneys. Fever, leukocytosis, albuminuria, oliguria, and anuria were associated. None of the findings was regarded as pathognomonic of the lesion. Pain was not a feature in young children, but, apart from this, Hepler's findings are in accord with those present in our cases. Campbell and Matthews [7] summarized what is probably the most reasonable approach to the disease by saying: "The clinical picture is that of overwhelming sepsis and toxemia consequent to the major initial condition . . . demonstration of albumin, pus, and blood in the urine should arouse more than a passing suspicion." They stated that it was possible to make a definitive ante-mortem diagnosis by the use of retrograde pyelography. One might add that the appearance of abdominal masses is of major importance with reference to the ante-mortem diagnosis. Whether masses are present or not, urinalysis in severely ill infants may give information concerning the existence of renal hemorrhagic infarction with more constancy than has heretofore been reported.

Pathologic Aspects

The pathologic findings in this group of cases were marked by infections at sites distant from the kidneys. These were otitis media, peribronchitis and interstitial pneumonitis, bronchopneumonia, and alveolar pneumonia. The gastro-intestinal tract showed no lesions in any case. Evidence of renal infection was notably absent in all but one case (case 2), in which a low grade cystitis, ureteritis, and minimal pyelonephritis were present. However, the vein walls were not involved in the inflammatory process in the kidneys, so it may be concluded that phlebitis did not play a part in the development of the thrombi.

Renal infarction was bilateral in 2 cases and was present in only the right kidney in the other 2. It was hemorrhagic in character. In

the cases of short duration, the lesion consisted of a patchy capillary and venular hyperemia and of hemorrhage in the region of the corticomedullary junction, compressing the tubules and causing early degenerative and necrotic changes in them. In the later lesions the whole medulla and most of the inner cortical structure were obliterated by hemorrhage, and, where the tubules were visible, necrosis of the epithelium was extensive. In the case of longest duration, almost the entire cortex showed coagulative necrosis while liquefaction had occurred in focal areas of the cortex and near the tips of the pyramids. No bacteria were seen in these areas. Growth of granulation tissue into the cortex from the capsule accompanied by a marked infiltration of neutrophilic leukocytes was observed in this case. In addition, the kidneys were adherent to the neighboring serosal surfaces of the colon.

Thrombosis of the main renal veins and of their largest branches was seen grossly. In one case the vena cava also was thrombosed and occluded. Microscopic examination revealed that in all cases the smaller intrarenal veins of the order of size of arcuate, interlobular, and, even in some instances, venulae rectae, were also the seat of thrombosis. Organization, when present, was more advanced in the smaller veins than in the larger ones, indicating that thrombosis began in the smaller intrarenal veins and spread to the main veins secondarily. In the case in which the inferior vena cava was occluded by thrombosis, the microscopic structure of the thrombi suggested that the process had begun in the small veins of the left kidney, extended into the main renal vein on the same side, and thence to the inferior vena cava and the right main renal vein. Thus bilateral involvement may occur as a result not only of simultaneous occurrence of thrombosis of small vessels of both kidneys, but by a retrograde involvement after thrombosis of the inferior vena cava. Arteries of all cases were free of thrombi except in case 2 in which a large branch of the main renal artery contained a thrombus much more recent than that in the vein and associated with peripelvic inflammation.

Evidence of embolism or thrombosis was present in the lungs in 3 cases in which pulmonary arteries, veins, and venules showed both recent and organizing thrombi. In one case the adrenal vein contained a very recent thrombus, and in another, thrombosis of the right saphenous vein had resulted in early gangrene of the foot.

The etiologic factors underlying thrombotic phenomena in general are not very well understood. In circumstances such as exist in the present series of cases, it is important to decide whether the thrombi

were initiated by thrombophlebitis originating from urinary tract infection. Infection seems to be excluded in our cases inasmuch as the vein walls were always free of inflammatory changes. Since local factors are not present to account for the thrombosis, one must consider systemic ones. The presence of thrombi in other organs tends to support the systemic approach.

It has been demonstrated by refined technics that the coagulability of the blood is increased in persons at rest in bed.[9,10] This is believed to be referable to an increased amount of circulating thromboplastin. The presence of infection and a surgical operation are accompanied also by increased coagulability,[11] as well as by increased rate of clot retraction.[10] Such widely used therapeutic agents as penicillin and streptomycin also have been shown to cause increased coagulability of the blood in animals. The effect is counteracted by dicoumarol.[12] It is interesting to speculate on the possible effect of dehydration on the coagulability of blood, for dehydration is so prominent a factor in some diseases of children. Certainly infection, immobilization, and dehydration were present in our cases at the time of the onset of the renal infarction.

In the absence of infection in the kidneys, thrombosis begins in the smaller veins. These are usually arcuate or interlobular veins, although veins of even smaller caliber may be involved. This is illustrated in our cases and those of Morison.[8] Following thrombosis of these vessels, the process spreads to the principal branches and to the main renal veins. The reasons for this localization have not, to our knowledge, been specifically studied. However, the complex mode of junction of the venulae recti with the interlobular and arcuate veins, as well as the veritable curtain of venous anastomoses at the corticomedullary junction,[13] suggests that anatomical factors may play a part, particularly since the earliest changes are noted in the region of the corticomedullary junction. If the circulation is already inefficient due to grave infection and dehydration, and the blood has an increased tendency to thrombosis, then stasis in this zone might be sufficient to determine the site for thrombosis. An analogous situation exists in primary (non-inflammatory) venous thrombosis of the dural sinuses where it is probable that anatomical peculiarities play a rôle in initiating thrombosis.[14]

It is difficult to assess the exact extent and distribution of thrombosis necessary to cause hemorrhagic infarction in cases studied by ordinary morphologic methods. However, as far as we can judge without hav-

ing studied serial sections in any of our cases, it appears that in order to cause massive infarction, thrombosis must involve the main renal vein, one or more of its main branches, or numerous small veins. This conclusion is supported by consideration of the cases collected from the literature by Hepler [2] in which 26 of 33 instances of hemorrhagic infarction of the kidneys were described as being the result of thrombosis of the entire venous tree, main renal veins, and large tributaries. Segmental infarction was observed to result from occlusion of a large direct branch of the main renal vein in 3 cases. There were 4 examples in which infarction occurred as a result of thrombosis of interlobular and arcuate veins alone, and 4 from thrombosis of smaller veins and capillaries. It has been reported also [3] that thrombosis of small venous radicles may occur without causing infarction. Nonocclusive thrombosis may be very extensive and still result in rather mild changes in the kidney parenchyma (Fig. 1).

That extensive occlusion of small and large veins is required to produce renal infarction may be explained by the fact that the efferent arteriole breaks up into a rich capillary network in which there is a free anastomosis between neighboring nephrons as has been demonstrated by neoprene casts of the kidney.[15,16] Thus, collateral channels are abundant and occlusion of large or numerous small veins is an expected requirement before serious interference with the nutrition of the parenchyma can occur. This state of affairs is in striking contrast to that which obtains in the arterial circulation where the occlusion of a single afferent arteriole is almost invariably accompanied by infarction of the glomerulus it supplies.

Once a sufficiently extensive thrombosis of veins has become established, capillary hyperemia occurs in the corticomedullary junction, medulla, and in patches of cortex whose blood is supplied almost entirely from the post-glomerular veins. This is soon followed by hemorrhage into the interstitial tissue with compression of the tubules. Degeneration and necrosis of the tubules follows and the whole medulla and inner cortex become a relatively homogeneous mass of necrotic tissue and laked red blood cells. Liquefaction may occur in foci, forming abscess-like cavities in which no bacteria can be demonstrated. The convoluted tubules in the outer two-thirds of the cortex eventually become necrotic in all but the immediately subcapsular zone and here, also, small areas of liquefactive necrosis may occur. A reactive inflammation and ingrowth of fibroblasts from the capsule and peripelvic tissues may follow if the patient lives long enough.

SUMMARY

Four cases of massive hemorrhagic renal infarction in children secondary to non-inflammatory thrombosis of renal veins form the clinical basis for this study.

The development of hemorrhagic infarction of the kidney in such cases appears to depend on occlusion of large veins or numerous small veins. In our cases thrombosis occurred first in the intrarenal venules and spread to the larger veins in a centripetal fashion.

It is suggested that venous thrombosis in these cases is related to increased coagulability of the blood under conditions of dehydration, infection, and bed rest, with the possible addition of anatomical factors concerned with the site of localization.

Ante-mortem diagnosis is difficult. The possibility of such a condition developing in children with sepsis accompanied by severe dehydration should always be kept in mind, with great importance being attached to the discovery of palpable kidney masses. The value of urinalysis in this condition may be greater than formerly suspected since few cases have been adequately examined in this respect. Apparently negligible abnormal findings in the urine may be of importance in the diagnosis.

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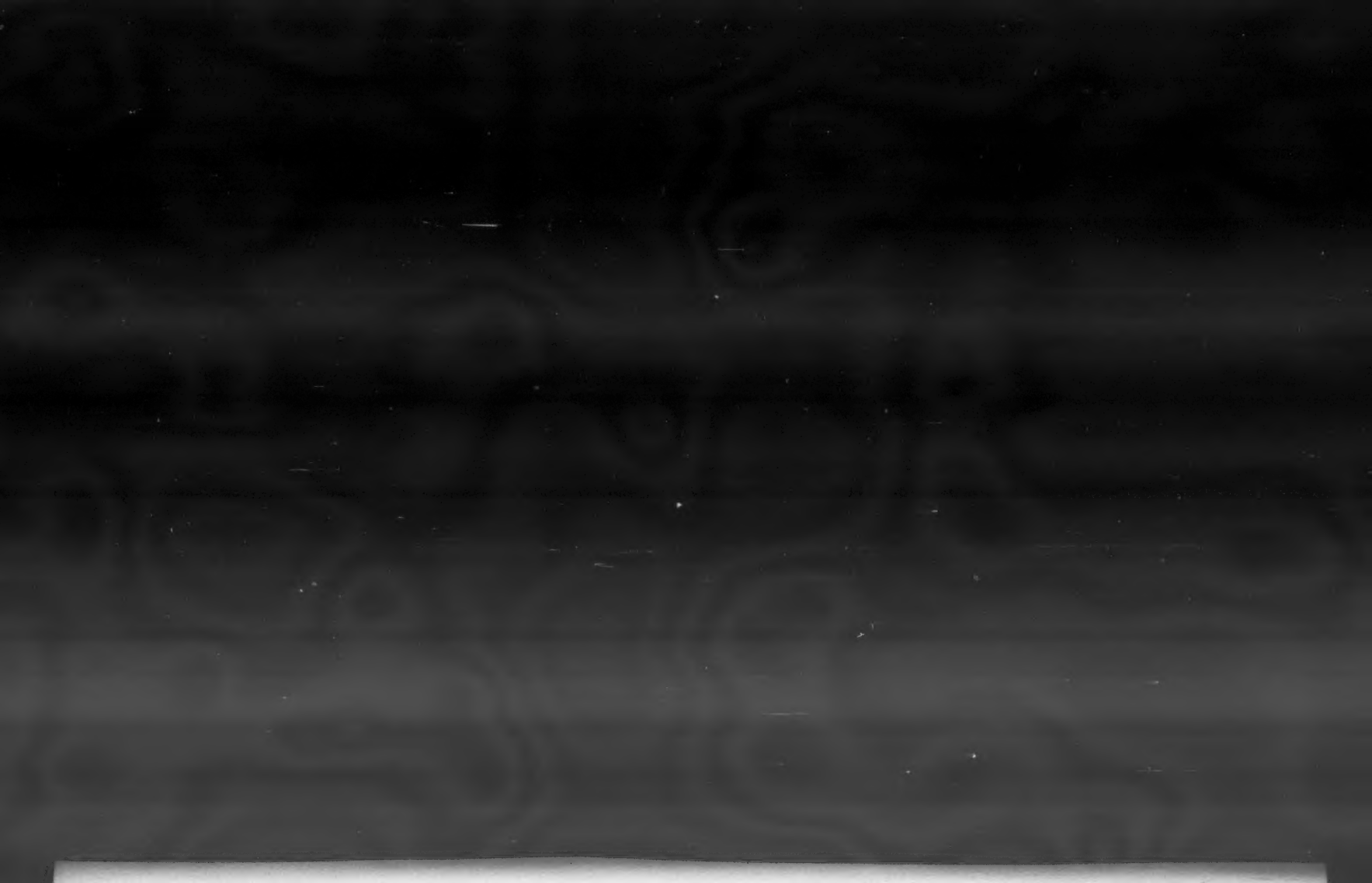
DESCRIPTION OF PLATES

PLATE 81

FIG. 1. Right kidney from case 1, showing patchy hemorrhage in the corticomedullary junction and on either side of it; also a non-occlusive, yellowish white thrombus with tapered end in the main renal vein.

FIG. 2. Left kidney from case 1, showing the striking appearance of the hemorrhagic pyramids and inner two-thirds of the cortex with strands of preserved cortical tissue. The pale thrombus occluding the main renal vein is shown cut obliquely.

FIG. 3. Case 4. Cortex of the right kidney showing recent thrombus in a small vein, marked interstitial hyperemia and hemorrhage, engorgement of glomeruli, and coagulative necrosis of epithelium of the convoluted tubules. The artery accompanying the vein is without thrombosis. Hematin, phloxine, and saffron stain. × 220.



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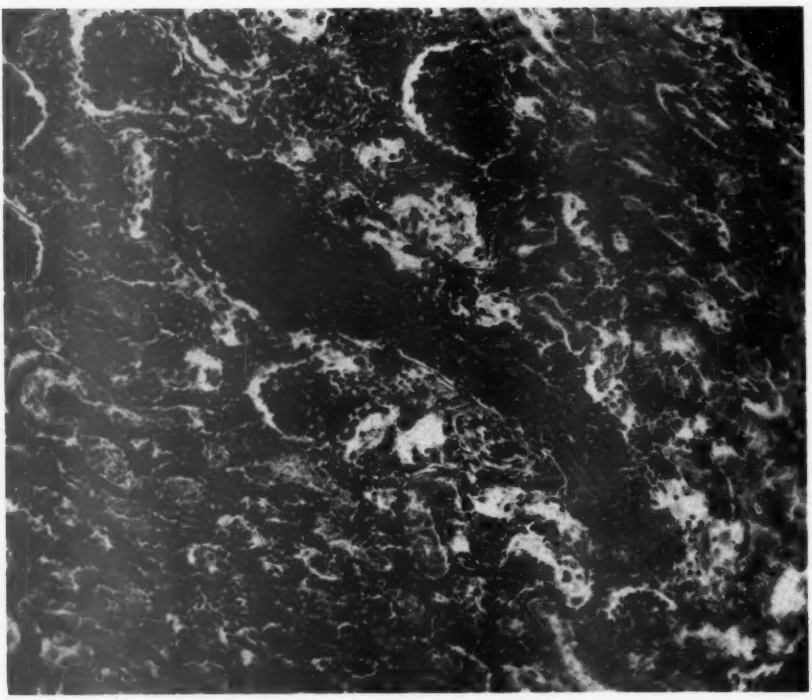


Kobernick, Moore, and Wiglesworth Venous Thrombosis with Renal Infarction

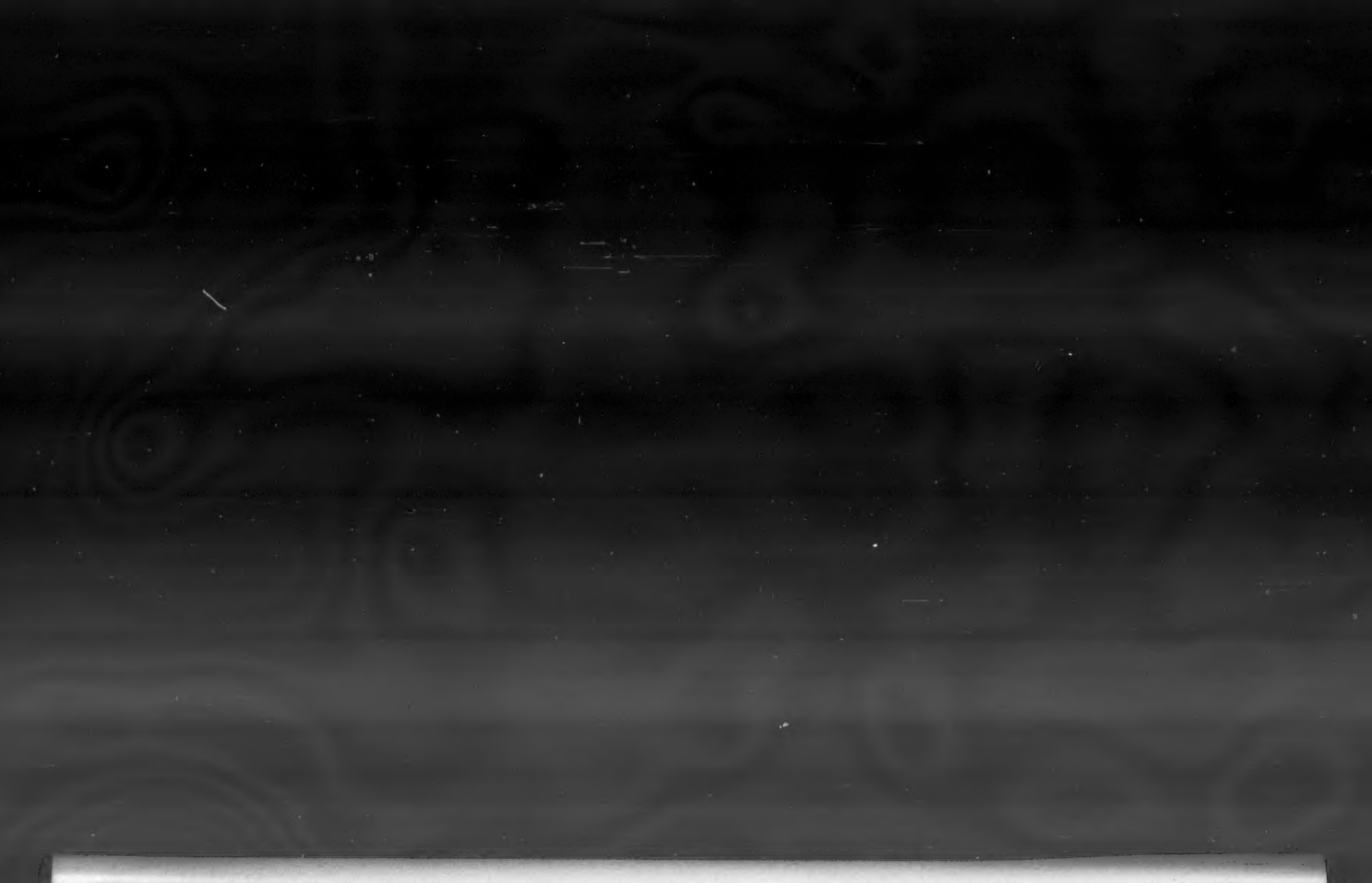
PLATE 82

FIG. 4. Section at the corticomedullary junction of the left kidney of case 1 as shown in Figure 2. An arcuate vein occluded by a thrombus with well advanced organization is present. Tangential section of an artery just below the vein contains degenerated blood elements but no thrombus. The cortex shows a zone of fairly good preservation on the left but obliteration by extravasated red cells is evident on the right. The whole medullary structure was obliterated by degenerating red cells. Hematoxylin and eosin stain. × 100.

FIG. 5. Longitudinal section of the main renal vein of the right kidney in case 1. The vein wall is below, separated in part from the thrombus (above) by two small clefts. The absence of evidence of inflammation and organization is evident. For comparison with the vein in Figure 4. Hematoxylin and eosin stain. × 102.

FIG. 6. Case 3. Right kidney. Section from the corticomedullary junction illustrating thrombosis of the arcuate vein with a patent artery. The thrombus shows early organization in its upper left edge. The cortex is relatively intact. The medulla shows extensive hemorrhage with vestiges of tubular structure present. The tubular epithelium of the medulla is necrotic. Hematin, phloxine, and saffron stain. × 102.

FIG. 7. Section of the main renal vein of the kidney of Figure 6 showing lamellated thrombus without evidence of organization. Hematoxylin and eosin stain. × 25.



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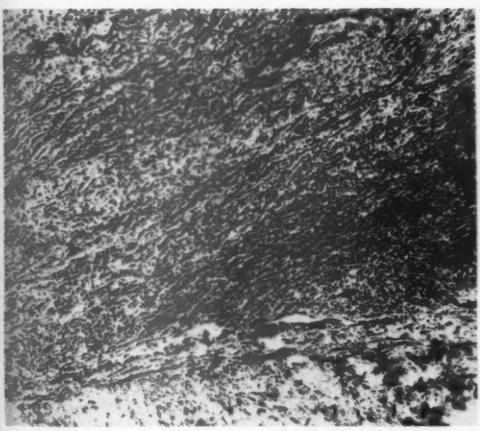

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Kobernick, Moore, and Wiglesworth

Venous Thrombosis with Renal Infarction

ELECTRON MICROSCOPE STUDIES OF COLLAGEN FROM NORMAL AND DISEASED TISSUES *

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Since the development of the electron microscope, considerable work has been done on the ultrastructure of collagen fibrils from various normal animal and human tissues. Frequent mention has been made of the possibility of showing structural change of fibrils in diseased tissues. The present study was undertaken for that purpose. Certain normal and diseased human tissues available in the laboratories of the Henry Ford Hospital during a period of 28 months were utilized for study. Additional studies were made on collagenous tissues from the rabbit and guinea-pig.

With present electron microscope technics, many factors limit the comprehensiveness of a comparative study of collagen fibrils from various sources. Cognizant of these limitations, I have proceeded in as direct a manner as possible to discover any structural differences that may exist between collagen fibrils from diseased tissues and from normal tissues as determined by the electron microscope. The work here presented is in no way sufficient to furnish final conclusions. The results of this investigation are presented as a contribution to a problem which will require considerable further work. Portions of a study of rabbit collagen are included, inasmuch as some of these electron micrographs show certain features of the ultrastructure of the collagen fibril to better advantage.

Earlier studies of connective tissue with the electron microscope revealed submicroscopic fibrils within an amorphous ground substance.[1] Alternating dark and light areas were found to recur along the long axis of the fibril in a relatively constant periodicity of about 640 Å.[2] This measurement agreed well with the "large fiber-axis" of collagen as determined by x-ray diffraction.[3] The dark bands measure about 440 Å, the light, 200 Å, and the two areas together constituted the macroperiod of the collagen fibril.[2] When the fibrils were stained with phosphotungstic acid, the dark bands appeared more prominent, with a greater quantity of stain taken up at these areas of the fibril as compared to the light areas.[2] Later studies revealed that under certain conditions a further differentiation of the macroperiod of the collagen

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fibril was manifested so that as many as six dark bands, alternating with light areas, were found.[4,5] Staining with osmic acid likewise revealed a differentiation of the collagen fibril into dark and light staining areas.[6,7]

A study of contour surface detail of the fibril became possible with the introduction of the metal shadowing technic of Williams and Wyckoff.[8,9] Intraperiod elevated rings were noted to recur along the long axis of the collagen fibril.[4,10] From two to six such elevated rings have been described within the macroperiod of the normal collagen fibril.[4,10] More often a "duplex" of elevated rings separated by an area of relative depression was noted, the number of distinct ring elevations found apparently depending on certain technical variations, possibly on an actual difference in structure, or possibly on a change in structure of the fibrils produced in preparation of the specimens for examination.

In shape, the collagen fibril as revealed by the electron microscope usually has been described as ribbon-like or as a flattened ellipse in transverse section.[2,4,6,7] The shape of the fibril in the fresh state has been open to conjecture inasmuch as preparation of specimens for electron microscopy requires dehydration and subjection to very low pressures. Preparations from fixed tissues have revealed essentially the same shape and contour as those from fresh tissues. Periodicity and general structure, except for some variations in width of the fibrils, have in general been reported to be the same for all animal and human collagenous tissues so far examined. The width of the fibrils in some preparations was strikingly uniform while fibrils from other tissues varied considerably in width.

Wyckoff [11] has shown electron micrographs of fibrils from connective tissue which he considered as differing from the regular collagen fibril. Wolpers [7] has described variation of the staining characteristics for fibrils from young persons and for fibrils from certain diseased rabbit tissues as compared to normal adult collagen fibrils, following the use of osmic acid.

Under certain conditions of acid-swelling, portions of collagen fibrils have been shown to split into a fine spray of minutely smaller filamentous structures.[11] Likewise in some preparations small fibrillar elements have been noted accompanying the larger regular fibrils; some of these small fibrillar elements have appeared to be splitting off from the larger fibrils, and are interpreted as units of which the larger fibrils are composed.[2]

When collagen fibrils are stretched under certain conditions, the

areas of smaller diameter (light staining portions) of the fibrils stretch more proportionately than do the (dark staining) areas of larger diameter.[2]

Tissue cultures have yielded fibrils[12] related to typical collagen fibrils, but in my opinion, judging from the electron micrograph reproductions presented, they are somewhat different in appearance.

Materials and Methods

Preliminary studies were made on the effect of certain fixatives and reagents on collagen fibrils as related to technics employed, using chiefly for this study a thin fascial sheet which is located between the subcutaneous tissue and musculature of the rabbit. A few such studies were made on collagen from a similar source in the guinea-pig.

Collagen fibrils were isolated from normal and diseased human tissues when the desired specimens became available in the hospital laboratory. Collagen was teased from desired areas of tissue under direct vision. The area for study was chosen by gross examination, supplemented by frozen sections or fixed sections of the general area from which the fibrils were isolated.

The areas from which human collagen fibrils were isolated for study were as follows:

Miscellaneous Sources. Infant tissue including peritoneum, pericardium, and Achilles tendon. Pleural adhesions and retroperitoneal tissue from a case of carcinomatosis. Fibrous scar of the heart from a case of arteriosclerotic heart disease. Keloid. Liver from case of portal cirrhosis.

Tumors. Neurofibroma of skin. Fibromas (2). Fibrosarcomas (3). Scirrhous carcinoma of breast. Wall of pseudomucinous cystadenoma of ovary.

Rheumatic Heart Disease (4 Cases). I. Mitral valve, endocardium of auricle, epicardium, and aorta, from a child, 5 years of age, with diffuse myocarditis and large Aschoff nodules throughout the myocardium and beneath the endocardium. II. Pleural adhesions, auricular endocardium, and mitral valve adjacent to area of calcification, from a male, 19 years of age, with chronic rheumatic fever with mitral stenosis, mural thrombi of the heart, extensive pleural adhesions, cardiac insufficiency, and generalized edema. III. Aortic valve, auricular endocardium, and capsule of shoulder joint, from a male, 36 years of age, who had had acute rheumatic fever when 7 years old, and who showed at necropsy calcifying aortic stenosis, myocardial hypertrophy, and focal interstitial edema and fibrosis of the myocardium. IV.

Pleural adhesions and auricular endocardium, from a male, 46 years of age, with mitral and aortic stenosis, mural cardiac thrombi, and subendocardial fibrosis with Aschoff nodules.

Disseminated Lupus Erythematosus (2 Cases). I. Dermis from area of a cutaneous lesion, pleural adhesions, thickened endocardium, and dura mater, from a female, 58 years of age, who had had skin lesions for 15 months, with verrucous lesions on the aortic valve, thickening of the endocardium, minimal glomerular lesions, and concentric periarteriolar fibrosis of the spleen. II. Pericardial and pleural adhesions from a girl, 13 years of age, ill for 18 months with dermal sensitivity to sunlight and with no response to salicylates, who showed at necropsy constrictive pericarditis, myocardial hypertrophy (600 gm.) and insufficiency, and degenerative changes of the small blood vessels in all organs.

Rheumatoid Arthritis. I. Rheumatoid nodules (2) surgically removed, with areas selected to show fibrinoid necrosis. II. Capsule of shoulder joint from a woman, 56 years of age, with generalized deforming arthritis.

Subacute Glomerulonephritis. Kidney capsule, edematous subcutaneous tissue, edematous gallbladder wall, and capsule of the shoulder joint, from a male, 17 years of age, with subacute glomerulonephritis, generalized edema, and focal myocarditis.

Technics

A number of technics were used in this study. That used most successfully and for most of the study consisted essentially in soaking the collagenous material in a 2 per cent solution of sodium bicarbonate, usually for about 30 hours, washing in running tap water and then in several changes of distilled water. The collagenous material was then teased out as thin as possible on a clean glass slide and, after drying, shadowed at an angle with chromium according to the method of Williams and Wyckoff.[8,9] Some materials were stained with phosphotungstic acid according to the methods of Schmitt, Hall, and Jakus [2] instead of shadowing. After shadowing or staining, the slide with the specimen in place was dipped in a 0.5 per cent solution of formvar * and, after drying, screen grids were put into place over areas desired for examination. The specimen was then stripped from the glass slide and onto the grids by means of Scotch tape and the tape subsequently separated from the grids. An alternate method consisted of stripping the collagenous material from the glass slide onto the screen grids before shadowing the fibrils.

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Results

General Consideration

The appearance of collagen fibrils in this study was essentially as described elsewhere.[4,10] The periodicity of the fibrils of all tissues studied fell within the range of 525 Å to 725 Å in the shadowed preparations. This is within the range of values reported for normal collagen fibrils of the human skin by Gross and Schmitt.[4] Collagen fibrils as revealed by the electron microscope are of indefinite length and have been described as ribbon-like or as a flattened ellipse in transverse section.[2,4,6,7] The more typical fibrils, as revealed in chromium shadowed preparations, showed along their long axis a double ring, elevated area alternating with an area of relative depression (Fig. 1). The two rings of the elevated area were separated by a small depression and the area of relative depression between successive double ring elevated areas showed a small elevated ring in its midportion. These elevated ring structures continued about the entire circumference of the fibrils as manifested by identical structure whether the top or bottom surface of the dried fibril was examined. In some of the less satisfactory preparations only a single broad area of elevation separated by a narrower area of depression was seen, and occasionally further differentiation of the macroperiod of the fibril was noted in preparations which were more successfully cleansed of obstructing material. As many as three ring-like elevations were seen in the areas of usual two ring elevation and two rings in the area of relative depression rather than just one (Fig. 4). A suggestion of further structure sometimes was noted, but such structure was not definite.

Fibrils stained with phosphotungstic acid usually revealed only a dark staining area alternating with a light area in each macroperiod (Fig. 5), although occasional preparations showed further differentiation with up to five definite, dark-staining bands in the macroperiod and a suggestion of subdivision of some of the bands into further divisions.

Rabbit Collagen

In rabbit collagen some preparations were made by direct spreading of the tissue onto a glass slide without washing; the fibrils were frozen with liquid oxygen before drying, dehydrated while frozen, and shadowed with chromium directly. In these preparations most of the fibrils were covered with an amorphous ground substance so that their structure was obscured; however, certain of the fibrils were sufficiently cleared of covering materials so that structure was well made out. These fibrils showed the usual structure as described above. In addi-

tion to the collagen fibrils of typical size, which were relatively uniform (about 1,100 Å) in width in these preparations and had the typical periodicity of collagen fibrils (about 640 Å), smaller fibrillar elements were noted. Some of the smaller units apparently were related directly to the structure of the typical larger fibrils as described below. However, a few of the smallest fibrillar units present, while perhaps also related, did not show a definite relation so far as periodicity and structure were concerned. These smallest fibrillar elements were made up of a chain of small spherical bodies, each about 175 Å in diameter. A similar small fibrillar element of like size and periodicity was found in a preparation of rabbit collagen fixed in 70 per cent alcohol (Fig. 3).

It was noted that collagen fibrils from some tissues tended to split longitudinally into smaller fibrillar elements more readily than did the fibrils of other tissues. Some of the smaller fibrillar elements were found in nearly all tissues studied, although these smaller elements tended to be few in number in human tissues (Fig. 7). In some groups of the rabbit tissue they were especially abundant, the number apparently increasing with the time the tissue was allowed to remain in 2 per cent solution of sodium bicarbonate or in 10 per cent formalin. In some electron micrographs of rabbit collagen, fibrils were seen in the process of splitting into the smaller units (Fig. 2). In other electron micrographs the smaller fibrillar elements remained aligned in a parallel manner as if derived from a common fibril (Fig. 4). These smaller fibrillar elements in the shadowed preparations averaged about 200 Å in width (Figs. 2, 4, and 7), while in the preparations stained with phosphotungstic acid they measured 100 Å and below (Fig. 5). As noted above, these smaller fibrillar units apparently exist to some extent in the free state as evidenced by the presence of some similar elements in the directly smeared frozen preparations; however, it would seem beyond doubt that the smaller units found in Figures 2, 4, and 5 have resulted from a longitudinal splitting of the larger fibrils while in solution or washing.

Rabbit collagen fibrils left in a 2 per cent solution of sodium bicarbonate for 30 hours showed a slight narrowing, up to 100 to 200 Å. Fibrils of rabbit collagen from preparations left in a 2 per cent solution of sodium bicarbonate for 72 hours showed an average narrowing of about 300 to 400 Å. In neither of these preparations was a change in periodicity noted and the structure of the fibrils did not appear altered. Likewise rabbit collagen fibrils remaining in 10 per cent formalin showed narrowing; one preparation kept in formalin for a period of 20 days showed a narrowing of the fibrils of about 400 to 500 Å. Here, likewise, the periodicity and the ring structure along the fibril

did not appear altered. It is not possible to evaluate entirely the narrowing of the fibrils in either of the cases cited, inasmuch as along with the narrowing of the fibrils there was a general increase of the smaller fibrillar elements which apparently had resulted from a longitudinal splitting of some fibrils. Whether the fibrils had undergone a lateral shrinkage or merely had all lost a portion of their width by splitting off of the smaller fibrillar elements must be left to further investigation.

Human Collagen Studies

It has been my purpose to investigate collagen fibrils from various human tissues involved in diseases with the possibility of finding actual variations in structure and periodicity of the fibrils. It is significant that in most of the reported studies, collagen fibrils from the various tissues of the same person, as well as of individuals of other species, including the lower forms of animal life, have been reported of the same structure and periodicity. If variations in structure or periodicity of fibrils from diseased tissues had been found in these studies, more extensive studies of normal controls of each of the specific tissues involved would be indicated to rule out normal variation in the respective tissues. Having found no real variation in structure or periodicity of the fibrils from the diseased tissues so far studied, there has been no need for exhaustive control studies of each of the specific tissues in so far as structure of the fibrils and periodicity are concerned. Some variation in width and size of the characteristic fibrils of various tissues and species does exist and unfortunately the normal variations in characteristic sizes, and limits of such variations, have not been established for most of these tissues. The scope of establishing such limits of variation in size of fibrils in the normal of the many tissues included in this study is a task greater than could be undertaken. Thus any final conclusion concerning a variation from the normal in the size of fibrils of the diseased tissues in this study must await more extensive investigation. The characteristic widths of fibrils as obtained in these studies are reported with this reservation in mind.

The actual measurement of widths of fibrils is not entirely satisfactory. Collagen fibrils as seen under the electron microscope often are arranged in bundles and, when so arranged, are normally aligned so that the periods of one fibril are in phase with those of the next and the line of boundary between the two fibrils is not always made out. Likewise fibrils are capable of splitting longitudinally into smaller elements almost indefinitely. Furthermore, when fibrils are partially covered by amorphous débris, they often appear to be narrower than accompanying single, well cleansed fibrils. This may be explained in

part by a partial covering up of the fibrils by the amorphous media, although it may be due also to the fact that fibrils, when partly supported by amorphous material, do not flatten out as much when drying as do cleansed fibrils which have no support. Often a fibril is noted to broaden at the point where it passes over a small elevation, such as another fibril.

With the exception of the smaller fibrillar elements (Figs. 4 and 7) which were found to some extent in most preparations, the fibrils in shadowed preparations from most of the human tissues measured between 700 and 1,200 Å in width with an average of about 800 to 900 Å. Exceptions to these measurements are noted below. In many tissues the fibrils were relatively uniform in size while in others they varied considerably. The smaller fibrillar elements, which averaged about 200 Å in width in the shadowed preparations, failed to show all of the characteristic structure of collagen fibrils and were considered a derivative or component of the fibrils rather than true fibrils.

Collagen fibrils isolated from infant peritoneum (Fig. 6), pericardium, and Achilles tendon were all of essentially the same size, measuring between 750 and 1,000 Å in width. Fibrils isolated from adult peritoneum were of a similar width.

Fibrils isolated from pleural adhesions (Figs. 7 and 8) showed considerable variation in width in some preparations whereas in others they were relatively uniform. Fibrils in this group varied between 450 and 1,300 Å.

Fibrils from keloid, fibrous scar of heart, and from a cirrhotic liver (Fig. 10) were relatively uniform in size, averaging about 850 Å in width.

Fibrils from benign fibroblastic tumors, including two fibromas and a neurofibroma of skin, showed relatively uniform fibrils measuring about 700 to 900 Å in width. Fibrils from a scirrhous carcinoma of the breast and fibrils from the wall of a pseudomucinous cystadenoma of the ovary were of similar size.

Fibrils were isolated from three fibrosarcomas. One of these, a fibromyxosarcoma of the spermatic cord, showed relatively uniform fibrils of about 850 Å in width. The second, a very well differentiated fibrosarcoma from the scapular area, showed relatively uniform fibrils of about 600 to 700 Å in width. The third, a fast growing, anaplastic fibrosarcoma from the belly of the triceps muscle, showed considerable variation in collagen production in various portions of the tumor. In some areas it was quite cellular, with giant cells and scant collagen production, and in other areas produced considerable collagen. Fibrils

were isolated from areas richest in collagen; the fibrils varied considerably in size (Fig. 11) with many extremely large fibrils measuring up to 2,300 Å in width, a number of medium-sized fibrils about 700 to 900 Å and still other fibrils down to several hundred Å in width. The largest fibrils from this neoplasm were the largest isolated from any tissue, so are of special interest. The structure and periodicity of all of the fibrils of the sarcoma appeared to be the same regardless of size.

Collagen fibrils were isolated from various tissues of 4 cases of rheumatic heart disease. In one the patient was a child, 5 years of age, who had a very severe acute attack with extremely numerous and large Aschoff nodules beneath the endocardium and throughout the myocardium. In the second, a male, 19 years old, apparently died of an acute exacerbation of chronic rheumatic heart disease. The other 2 were cases of rheumatic fever, possibly healed but with residual valvular scarring and stenosis. No variation in fibrillar structure or periodicity was noted in any of the tissues included (cf. outline of tissues used). Some of the fibrils from the child, especially from the endocardium, tended to be small, measuring between 400 and 600 Å in width.

Collagen fibrils were isolated from 2 cases of disseminated lupus erythematosus. A few fibrils of an involved skin area (Fig. 12) of the first case measured up to 1,700 Å in width. This exceeds the range given by Gross and Schmitt [4] for collagen of human skin in their studies of normal skin from 16 persons in various age groups. The average width of the fibrils of pleural adhesions in this individual was about 700 Å; those of the endocardium, about 800 Å; of the skin, 1,200 Å; and of dura, 1,300 Å. Fibrils from pericardial adhesions in the second case measured about 650 Å in width and from lung adhesions, 900 Å.

Fibrils were isolated from areas involved in "fibrinoid necrosis" of two surgically removed rheumatoid nodules. These fibrils were not unusual in structure or periodicity and measured about 600 to 700 Å in width.

Fibrils from the capsule of the shoulder joint of a patient with rheumatoid arthritis with generalized joint involvement and deformity showed no unusual feature and measured between 600 and 1,200 Å in width (Fig. 9).

Fibrils were isolated from subcutaneous tissue, shoulder joint, kidney capsule, and gallbladder wall of a case of subacute glomerulonephritis with generalized edema. Fibrils were relatively uniform and did not vary significantly in the various tissues included, measuring between 700 and 1,200 Å with an average of about 900 Å.

Discussion

In the present study I have undertaken to isolate fibrils from diseased tissue to find, if possible, direct evidence of structural change and change in periodicity as compared with fibrils from uninvolved tissues. Were fibrils to be converted directly from their usual structure into amorphous non-fibrillar material, my methods could hardly be expected to detect such change unless indirectly by the failure to find fibrils.

Obviously a more direct selection of fibrils, with the possibility of selecting fibrils directly from a microscopic area involved in "fibrinoid necrosis," would be desirable in a study of collagen in disease. Such selection of fibrils may be possible eventually, with further development of the ultrathin sectioning microtome. Technics used in this study allowed only for an isolation of fibrils from a general area, although this area may be relatively small. In spreading fibrils from the area of selection only a small percentage of fibrils are suitable for examination; some fibrils may be covered by others or amorphous material or may be so oriented when shadowed with metal that maximum detail is not brought out. Furthermore, for adequate interpretation all fields for study must be photographed. These factors, added to the high magnifications used with the electron microscope, limit considerably the amount of any specimen that may be examined adequately. By the methods used in this study there was a probability of finding abnormal fibrils, if such were present, although failure to find abnormal forms does not permit a conclusion that abnormal forms did not exist. Abnormal forms may merely have escaped examination and only by repeated studies with similar results will final conclusions be derived.

The chief obstacle to a study of any collagenous tissue by means of the electron microscope is the presence of an amorphous ground substance covering the surface of the fibrils to varying degrees. This substance, particularly when using the metal shadowing technic, must be removed, for unless the surfaces of the fibrils are clean, chromium or other metals will be deposited on the covering material rather than the true surface of the fibril and a study of surface detail of the fibrils will not be possible. Occasionally, collagenous material may be spread so thin that some of the fibrils are relatively free of the covering material; this is generally not true, however, and the amorphous material must be washed from the fibrils. A number of substances have been used in attempting to remove it, although apparently none with uniform success. Most of my materials were soaked in a solution of 2

per cent sodium bicarbonate prior to washing in water. This became a standard procedure because of its apparent aid in rendering some tissues more readily freed of the amorphous materials in washing. Fibrils of loose and edematous areolar tissues in general responded more successfully than the more compact tissues.

My experience with stained preparations has been limited inasmuch as I was unable to secure to a satisfactory degree uniform and maximum staining of the same materials on successive trials. I have made no studies of preparations stained with osmic acid and am not qualified to evaluate an unusual staining quality of infant collagen fibrils and fibrils from certain diseased tissues of the rabbit as reported by Wolpers.[7] I have found no variation in fibrillar structure in infantile or diseased tissues by the shadowing technic.

The significance of fibril size is not known. Fibrils in the free state before fragmentation and spreading of the parent tissue appear, for the most part, to be arranged in bundles. Even in many electron micrographs, groupings of the fibrils are noted. In such groups the fibrils usually are arranged so that corresponding areas of the macroperiod of one fibril are in phase with those of its neighbor and the lateral boundaries of individual fibrils may not always be made out. Likewise, fibrils are capable of almost indefinite longitudinal splitting into smaller elements. Thus fibril size as noted in electron micrographs may or may not be a characteristic or peculiarity of the particular tissue in study; preparation of the specimen and likewise the accompanying amorphous ground substance may have a bearing on the size of fibrils and the ease with which they are split into their component parts.

Summary

Collagen fibrils were isolated from normal and diseased human tissues including benign fibroblastic tumors, fibrosarcomas, fibrous adhesions, fibrous scar of heart, keloid, cirrhotic liver, and from a number of sources in cases of the so-called collagen diseases. This latter group consisted of 4 cases of rheumatic fever, 2 cases of disseminated lupus erythematosus, 3 cases of rheumatoid arthritis, and a case of subacute glomerulonephritis. The metal shadowing technic of Williams and Wyckoff [8,9] was used almost entirely in this study.

Collagen fibrils vary in size in both normal and diseased tissues. The limits and the significance of such variations are not yet established. In one case of fibrosarcoma, fibrils of many sizes were found; of particular interest in this case were fibrils which measured up to 2,300 Å in width. These large fibrils were the largest isolated in any

of the tissues of this study. A few fibrils from an involved skin area in a case of disseminated lupus erythematosus measured up to 1,700 Å in width. This exceeds the range of fibril widths established by Gross and Schmitt [4] for fibrils of human skin isolated in 16 necropsy cases in which the skin was considered uninvolved by any disease. Much work is yet to be done before definite conclusions can be drawn regarding possible changes of collagen fibrils in disease. No significant change in structural characteristics and no change in periodicity of the fibrils could be demonstrated in the diseased tissues used in this study.

This investigation was conducted with the technical assistance of Ruth M. Sturrock, M.S., and Helen Woods.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 83

FIG. 1. Rabbit collagen fibrils shadowed with chromium at a 45° angle. Elevated ring structures are seen to recur in a definite sequence along the long axis of the fibril. Double ring elevated areas are noted, separated by a shorter area of relative depression. These two areas together constitute the macroperiod of the collagen fibril. A small elevated ring is noted in the area of relative depression; a small area of depression is seen between the two rings of the elevated area. Seven or eight linear markings are noted to course the long axis of the vertical fibrils on the right side of the picture. These are best seen when the picture is viewed turned at right angles. Small nodulations are noted between these lines at each elevated ring. Tissue was in a 2 per cent solution of sodium bicarbonate 30 hours prior to washing. × 85,700.

FIG. 2. Rabbit collagen fibrils shadowed with chromium at a 45° angle. Of note are the large fibrils as seen in Figure 1 and one fibril running transversely at the left side of the picture splitting into smaller fibrillar elements. Some of the structures of the larger fibrils remain in the smaller elements. Preparation is the same as for Figure 1. × 31,000.

FIG. 3. Rabbit collagen fibrils shadowed with chromium at a 10° angle. Three orders of fibrils are present. The intraperiod structure of the larger fibrils is not well shown. Second order fibrils measure up to 400 Å in width. Periodicity measures slightly less in this preparation than in the larger fibrils. A fibril of the third order is present in the lower midportion of the area, running off at an angle from the right end of the lowermost medium-sized fibril. This fibril is made up of small recurring spherical bodies of about 175 Å in diameter with no pattern corresponding to that of the larger fibrils. Considerable graininess in background is due apparently to chromium. Material in 70 per cent alcohol 18 hours prior to washing. × 69,600.

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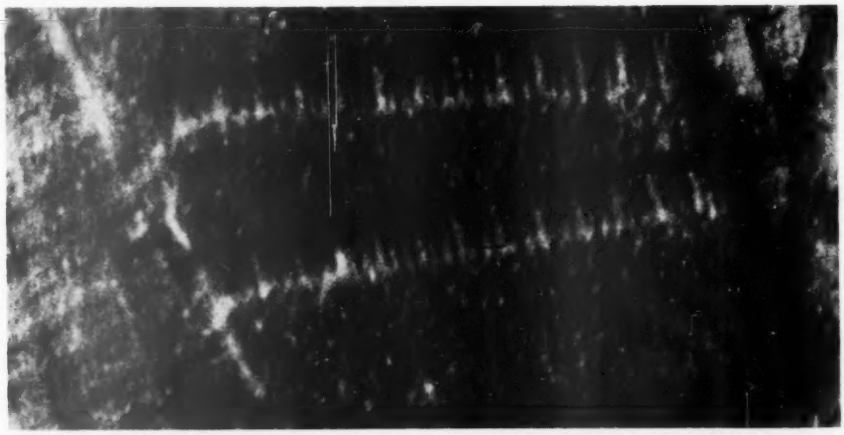

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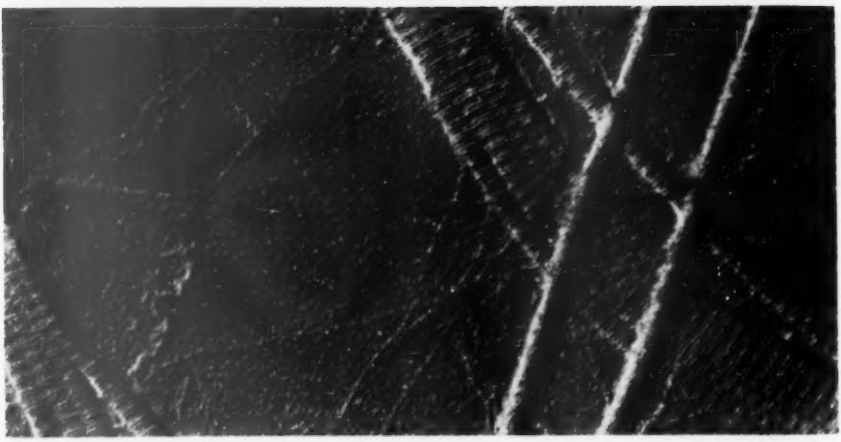

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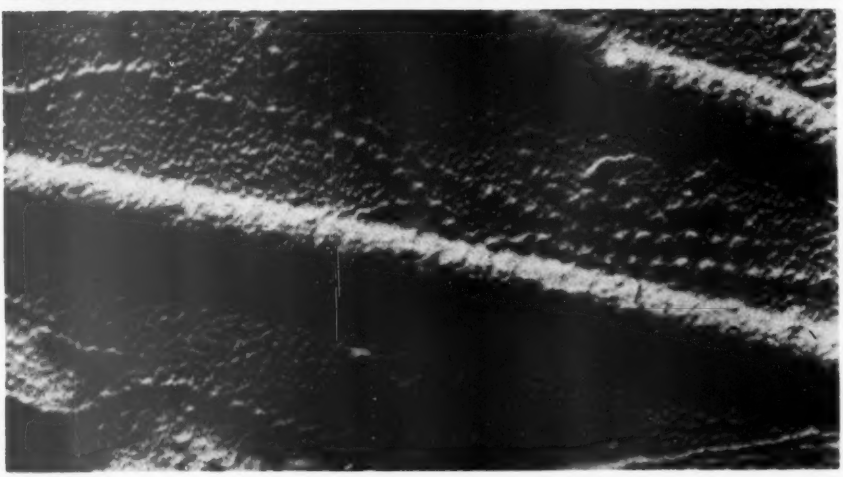
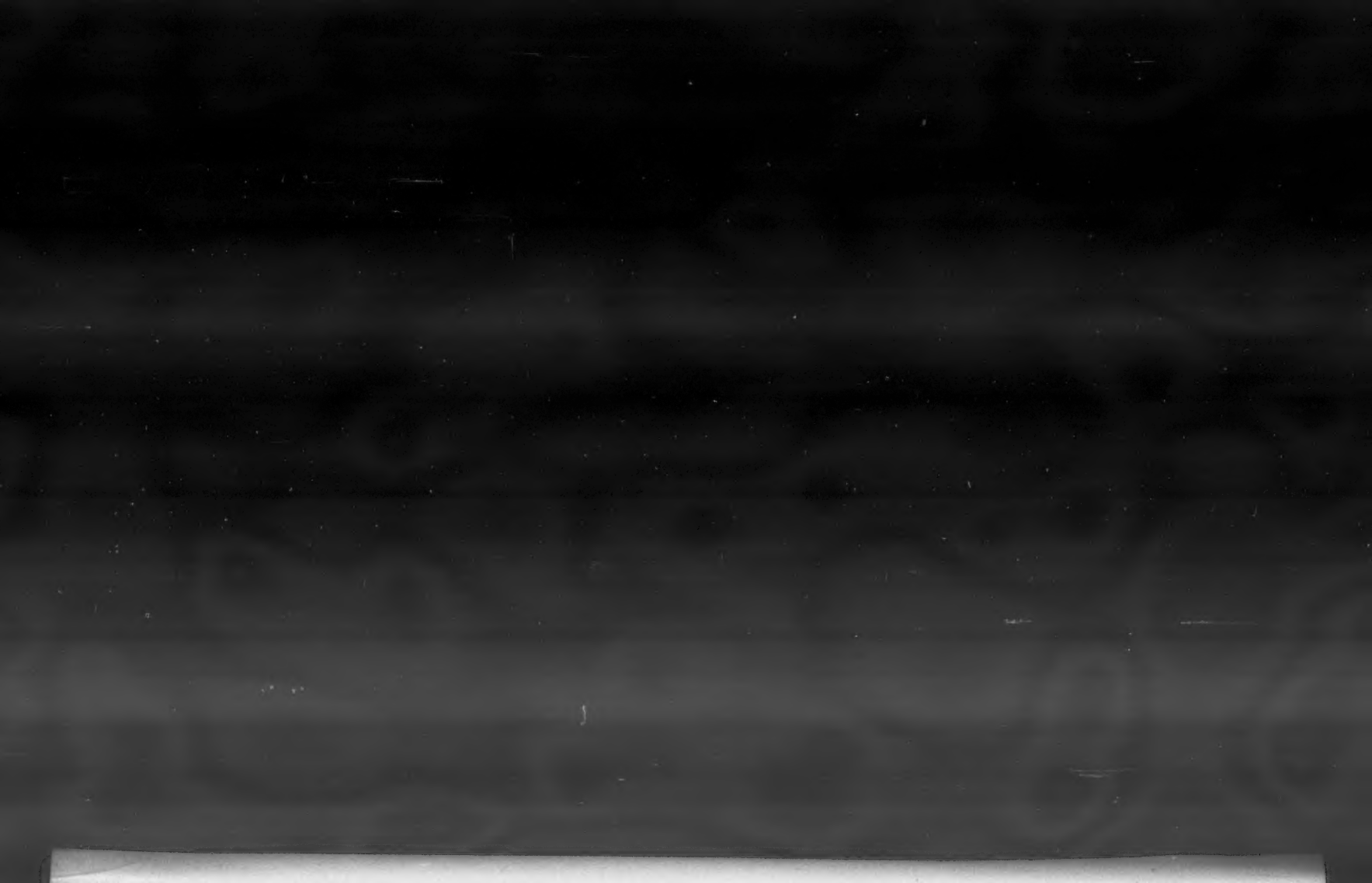


PLATE 84

FIG. 4. Rabbit collagen shadowed with chromium at a 45° angle. Same technic as for Figures 1 and 2 except that this tissue was in a 2 per cent solution of sodium bicarbonate for 72 hours before washing. Large fibrils and smaller fibrillar elements are present as seen in Figure 2. The large fibrils are slightly narrower than in Figure 3 but with the same intraperiod structure. In some of the fibrils five intraperiod rings are made out. Smaller fibrillar elements are about 200 Å and less in width. Many of the smaller fibrillar elements remain aligned as if they were derived from a common larger fibril. Some intraperiod structure is evident on the smaller fibrillar elements. × 31,000.

FIG. 5. Rabbit collagen fibrils. Same material as seen in Figure 4 except it is stained instead of shadowed. Large fibrils have essentially the same periodicity as the fibrils in Figure 4. The macroperiod is made up of a dark and a light staining area. Small fibrillar elements measure down to 100 Å and less in thickness. Smaller fibrillar elements are slightly stretched as compared with those in Figure 4. Phosphotungstic acid stain. × 31,000.



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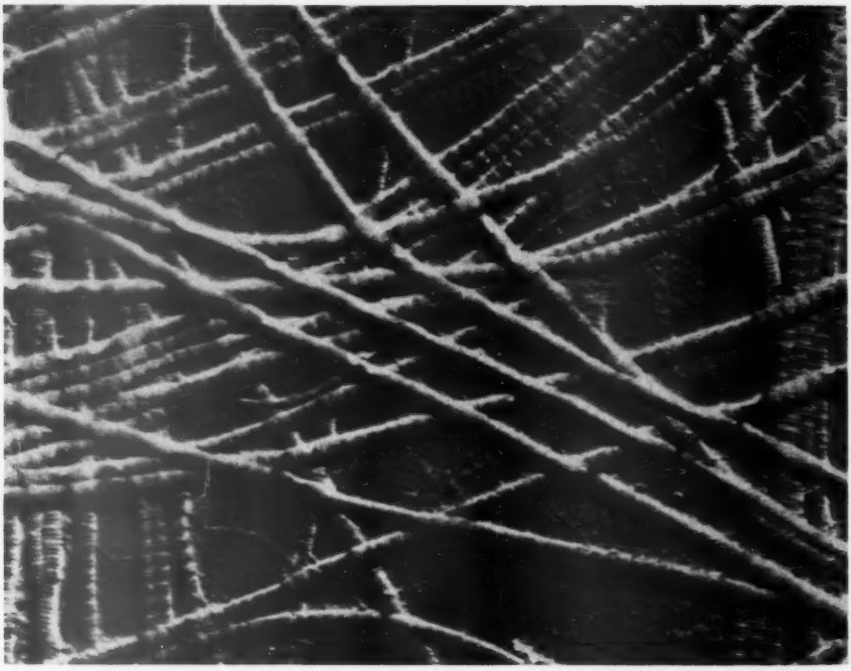

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PLATE 85

FIG. 6. Human collagen fibrils from the peritoneum of a stillborn infant, shadowed with chromium at a 45° angle. Material was in a 2 per cent solution of sodium bicarbonate for 30 hours before washing. × 66,300.

FIG. 7. Human collagen from pleural adhesions from case of carcinomatosis, shadowed with chromium at a 45° angle. There are small fibrillar elements, about 200 Å in width, with essentially the same periodicity as the larger fibrils. Material was in 2 per cent sodium bicarbonate 30 hours before washing. × 37,500.

FIG. 8. Human collagen from pleural adhesions from a case of chronic rheumatic fever in a 19-year-old male. Shadowed with chromium at a 45° angle. Material was in 2 per cent sodium bicarbonate for 30 hours before washing. × 34,000.

FIG. 9. Human collagen from shoulder joint capsule of a case of rheumatoid arthritis in a 56-year-old female with generalized joint involvement and deformity. Shadowed with chromium at a 20° angle. Normal ring structures present with small nodulations evident on some of the ring elevations. Material was in 2 per cent sodium bicarbonate 24 hours before washing. × 57,000.

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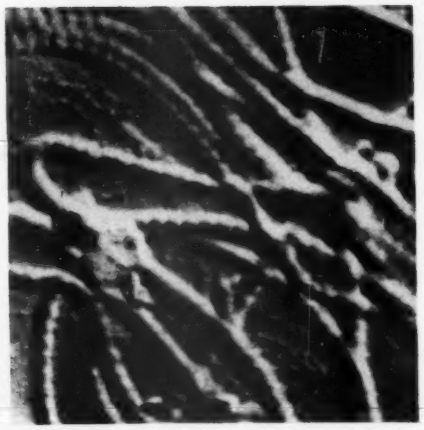

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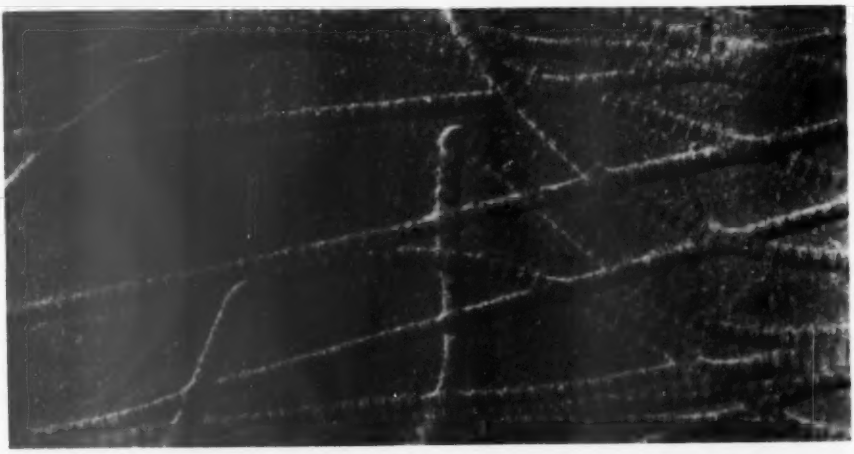

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PLATE 86

FIG. 10. Human collagen fibrils from fibrous area of a liver with portal cirrhosis. Shadowed with chromium at a 45° angle. Material was in 2 per cent sodium bicarbonate ½ hour before washing. × 66,800.

FIG. 11. Human collagen fibrils from a fibrosarcoma originating in region of triceps muscle. Shadowed with chromium at a 45° angle. Fibrils vary considerably in width, ranging from below 300 Å to over 2,000 Å. All fibrils appear to have the same general structure and periodicity. Material in 2 per cent sodium bicarbonate 30 hours before washing. × 25,800.

FIG. 12. Human collagen fibrils from dermis from involved area in a case of disseminated lupus erythematosus. Shadowed with chromium at a 20° angle after stripping from glass slide onto screen grid. In addition to fibrils, a replica structure is evident in the upper portion of the picture, representing an area from which a fibril has been lost in stripping. Fibrils as shown measure about 1,250 Å in width. A few fibrils in this preparation measured up to 1,700 Å. Material was in 2 per cent sodium bicarbonate 30 hours before washing. × 73,500.

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HISTOPATHOLOGY AND ETIOLOGY OF PNEUMONIA IN CHILDREN DYING AFTER ANTIBACTERIAL THERAPY *

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The introduction of effective sulfonamides and antibiotics, and especially penicillin, into the therapeutic management of pneumonia has altered dramatically the clinical course of this disease. With the widespread use of these drugs, death from bacterial infections of the respiratory tract now rarely occurs in adults, and in children fatalities have been markedly reduced. The decrease in mortality rate is strikingly illustrated in the statistics of the Children's Hospital of Pittsburgh where, during the years 1939 to 1949 inclusive, the death rate gradually fell from 7.1 per cent of admissions to 2.8 per cent. Paralleling the decline in mortality rate, there was a salutary change in the clinical picture, apparently due to some treatment before admission. Children with upper respiratory involvement showed coryza, fever, cough, dyspnea, and occasionally convulsions. Sometimes a few crepitant râles were heard but rarely was there any definite sign of consolidation. Roentgenograms of the lung revealed little change except a slight increase in hilar shadows. Upon penicillin therapy following admission, the temperature usually fell to normal within 24 hours and a marked improvement in the clinical condition was noted. Hospitalization ranged from 2 to 5 days. Fatal cases were limited generally to infants 2 or 3 weeks old, or to children with some additional disease. In the past 10 years we have examined lungs grossly and histologically from approximately 250 children who died from pneumonia *per se* and from about 450 other children who died from different causes but showed also a complicating terminal pneumonia. In cases terminating fatally, the pulmonary lesions found at necropsy were different from those seen previously by one of us [1] and have stimulated these studies on the histopathology and possible etiology.

Because the pneumonia was atypical and few if any bacteria could be found on cultures of lungs made post mortem on ordinary mediums, a viral etiology, possibly influenza virus, was suspected. Considerable difficulty was encountered in proving a viral origin and the etiology of the pneumonia is still not clear. Whether the tissue changes have been evoked by residual toxins of bacteria removed from the field by sulfonamides and antibiotics or are due to an unidentified virus remains unanswered.

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Parker, Jolliffe, Barnes, and Finland [2] described the pathologic changes in 5 lungs of adults from which an influenza virus was isolated. Two of their cases were bacteria-free. These authors stated that they found only 3 earlier reports [3-5] containing a description of pulmonary alterations associated with influenza virus. Straub and Mulder [6] described the lungs from a patient dying with bronchopneumonia in addition to a complicating empyema and from whose sputum influenza virus A was obtained. The patient's serum withdrawn between the fourth and eighth days showed an increase in antibody titer for the W. S. strain of influenza virus A. *Staphylococcus aureus* and *Streptococcus haemolyticus* were cultured from the sputum and empyemic pus. Mulder and Verdonk [7] also reported a case in which influenza virus A was obtained from the lungs of a patient dying with pneumonia, and discussed possible pathogenesis. Recently, Maxwell, Ward, and Van Metre [8] recovered influenza virus four times from cultures of lungs of 46 patients with pneumonia. Two of the patients with positive cultures were listed as infants. Only a brief resumé of pathologic findings was included. These authors all stressed the bronchial lesions.

Morphologic Studies

Necropsies were performed in the majority of the cases within 2 hours after death. Grossly, the lungs were of three types, depending upon the severity of the infection. With the mildest infection, the lungs showed only a slight congestion. With a moderate grade of involvement the lungs presented a more marked congestion but were crepitant except for occasional small, subpleural, hemorrhagic areas measuring from 5 to 8 mm. in diameter. In the acute type, all lobes showed some patchy, discrete areas of hemorrhagic infiltration, but the areas most affected were the dependent posterior parts of the lower lobes. In about 20 per cent of the cases, both lungs showed a generalized hyperemia. The organs appeared soggy, heavier than normal, although they floated in water, and the cut surface exuded a thin, bloody fluid. No pleurisy was observed.

The histologic lesions, primarily interstitial, likewise varied in intensity and could be divided roughly into two groups. In the milder type the changes were restricted to the alveolar wall, but the more fulminating type exhibited in addition an exudate of serum or blood in the alveoli.

The earliest lesions occurred in patchy areas in which the width of the alveolar walls was increased by cellular proliferation from two to

six fold (Figs. 1 and 2). The hyperplasia continued until all of the alveolar walls were involved (Fig. 3). As the process advanced, areas developed in which the alveolar walls became so thickened that the air spaces were impinged upon and markedly reduced. In a few instances the lining epithelium was hypertrophied and the cells stood out like small beads which sometimes contained brownish hemoglobin pigment. Throughout the involved lung fields, the bronchi were not affected and respiratory ducts remained intact as clear, round spaces (Fig. 4) until they became obliterated because of pressure from the surrounding hyperplastic tissues. The proliferating cells were fairly uniform in size and appearance (Fig. 2). The nuclei ranged from a moderately vesicular to a somewhat pyknotic type and were surrounded by varying amounts of pink cytoplasm. The characteristic features of plasma cells were not observed. The origin of these cells could not be determined definitely, but they apparently arose *in situ*. Neutrophils invariably were absent. The capillaries sometimes were dilated and, rarely, a few red blood cells were found free in the tissues of the alveolar walls or in the air sacs. These milder interstitial reactions frequently occurred in terminal secondary pneumonias.

In the children who showed more acute pulmonary symptoms, exudative features predominated in the lung. To the cellular background already described was added an exudation of serum, plasma, and red cells (Figs. 5 and 6). This exudate was most marked when the infection occurred in infants during the first 48 hours of life, but was found also at later ages. The areas with hemorrhage frequently alternated with lung fields in which only the thickening of the alveolar wall was present. In the hemorrhagic areas, the cellular proliferation leading to thickening of the alveolar walls seldom reached the extreme degree which was observed in pneumonia of the milder type. The fluid exudate from the permeable capillary walls became extensive (Fig. 6). Free blood was found in the alveolar spaces but only rarely was it retained within the cellular tissues. The terminal respiratory ductules usually remained as clear spaces. The bronchi were nowhere involved. Many of the erythrocytes were hemolyzed or persisted as clumps of pigment. The endothelial cells lining the capillaries were thin and their nuclei flattened and pyknotic. Rarely, the small arterioles showed a hyperplastic endothelium. In the moderate cases an occasional pigment-filled macrocyte or so-called heart lesion cell was seen. When the infection was of long duration or more severe, patches of heart lesion cells were found in great numbers both *in situ* bordering thickened alveolar walls or free in the alveolar spaces (Figs. 7 and 9). In

the latter sites, these cells frequently were joined in flat sheets or long strands and had obviously been desquamated from the alveolar lining. These pigment-laden macrophages were especially numerous and prominent when chronic passive congestion of the lungs was superimposed clinically, and their derivation from the swollen epithelium lining the air sac was easily demonstrable. In such lungs the epithelium covering dilated capillaries frequently was so stretched and separated that the underlying vascular endothelium formed the alveolar lining in many places.

Hyaline alveolar membranes were a characteristic finding in the more severe cases and their origin from fluid exuding from capillaries was apparent from the examination of many lungs. They began initially as thin layers (Figs. 8 and 10), were sometimes of moderate width, and in a few instances were so extensive that they occluded the entire alveolar space. Occasionally they appeared finely granular. Such structures obviously completely precluded any interchange of gases in the lungs.

The septa and connective tissues frequently showed edema. It should be emphasized that the epithelial lining of the bronchi and bronchioles was intact and appeared fairly normal except in those cases in which bacteria, either penicillin-resistant or remaining in the lung because of inadequate dosage of penicillin, complicated the picture. With associated bacterial invasion the bronchial epithelium was eroded, frequently desquamated, and the lumina of the bronchioles contained a variable amount of acute cellular exudate. A few bacteria could then be demonstrated in tissues by the Gram stain but considerable difficulty was encountered in their isolation culturally after therapy with penicillin.

Bacteriologic, Virologic, and Serologic Studies

Studies made to determine causal agents included bacterial cultures, and attempts to isolate a virus from lung tissues post mortem. In addition, tests were carried out for influenza virus antibody, agglutinations against streptococcus MG, and cold agglutinins.

From most of the lungs of children dying of pneumonia in the hospital, bacteria were eliminated clinically by adequate antibiotic treatment. For the past 3 or 4 years throughout the Pittsburgh district the therapeutic use of penicillin and sulfa drugs has been fairly widespread and many patients on admission to the Children's Hospital had already received antibiotic therapy. In the hospital not only penicillin but aureomycin, chloromycetin, streptomycin, and dihydrostreptomycin, when indicated, were employed. On examination of direct

smears from the lung, stained by Gram's technic, one might encounter only an occasional organism after prolonged searching. Routine post-mortem bacterial cultures from pieces of lung removed aseptically when the chest was first opened have been negative in most cases, in sharp contrast to the experience of Menten *et al.*[1] before the era of antibacterial agents. The few bacteria isolated were mainly *Staphylococcus aureus* and *albus*, and *Streptococcus viridans*.

During the late autumn of 1947 and the first 4 months of 1948, blood taken from children admitted to the hospital with upper respiratory infection and signs of pulmonary involvement yielded in some instances serologic evidence of infection with influenza virus, type A. The sera from these children were tested in the Virus Research Laboratory of the University of Pittsburgh School of Medicine. The antigens used for the hemagglutination inhibition test for antibody were the PR8 and FM1 strains of influenza virus A and the Lee strain of influenza virus B. The results of these studies will be reported elsewhere by Drs. J. E. Salk and M. L. Bailey. During this period, namely, the winter of 1947–48, 30 necropsies, in 8 of which the major anatomical diagnosis was atypical pneumonia of unknown origin, were performed. Attempts were made to culture influenza virus from 6 of the 8 post-mortem lungs in which the gross appearance suggested a possible virus involvement. A suspension of the lungs, to which was added penicillin and streptomycin prior to inoculation into the amniotic sac of 12 or 13-day-old chick embryos, gave negative results. During the winters of 1948–49 and 1949–50 (that is, following the year when positive evidence for antibody against influenza virus A was obtained), sera taken from patients with pneumonia on admission to the hospital gave no serologic evidence for infection with influenza virus by the hemagglutination inhibition tests. Also, during the winter of 1949–50, lung tissue, submitted to the Virus Laboratory from 36 necropsies in which later microscopic examination showed interstitial pulmonary lesions with little or no acute cellular exudate, only once yielded a virus, namely, influenza virus type A. The lungs from which this influenza virus A was isolated, when cultured bacteriologically, gave a pneumococcus (not-typed), *Staphylococcus aureus, Staphylococcus albus, Micrococcus catarrhalis* and *Streptococcus viridans*. In the lungs of this patient neutrophils were present in the hyperplastic alveolar walls and in the alveoli.

Agglutination of streptococcus MG by the sera from 20 patients, carried out during the winter of 1948–49 and found to be positive in only a very small percentage of cases, was discontinued.

Cold agglutination tests, also performed during the winter of 1948–

49, were positive in approximately one-half of the patients, but as this procedure did not seem to have differential diagnostic significance it was not continued routinely.

Discussion

The tissue changes which we have described in lungs of children dying of pneumonia are due either to prolonged bacterial toxic action or to an additional infecting agent which persists and is active after the eradication of the bacteria. Few reports are found in the literature concerning the histopathologic changes in pneumonia from which bacteria have been entirely eliminated by adequate therapy. Because of the relatively high susceptibility of infants and young children to pulmonary infections, an opportunity was afforded us of studying a large number of such abacterial lungs. Two outstanding pathologic differences between abacterial pneumonic lungs and those in which bacteria were present have been observed by us. These were, first, a lack of acute cellular exudate throughout the bronchial tree and alveoli and, second, cellular hyperplasia which occurred in variable amounts in the alveolar walls. With complete disappearance of bacteria there was an absence of neutrophilic exudate, and the latter was observed only in those cases from which bacteria were obtained culturally or demonstrated by Gram's stain on smears from the lungs at necropsy or in fixed stained sections. The amount of acute cellular exudate appeared to be in direct proportion to the number of bacteria present.

An interstitial pneumonia of varying degree always was found. This interstitial hyperplasia might be limited to cellular increase in alveolar walls or might, in addition, be associated with an exudate of serum and blood into the air sacs, together with a variable number of heart lesion cells. In the more acute cases this serous exudate became prominent and was invariably associated with hemorrhage. The bronchi and bronchioles were free from involvement and their lining epithelium appeared normal. Evidence from a series of cases indicated that the exudation of fluid from the capillaries underlay the formation of the hyaline membrane. The gradual transformation of the finely granular precipitate to a homogeneous hyaline structure is believed to be due to a change in colloidal state of the plasma transudate.

The heart lesion cells undoubtedly have their origin from the cells of the alveolar wall. In several instances, and especially where chronic passive congestion intervened, we observed many swollen septal cells *in situ* lining the alveolar spaces and occasionally containing phagocytized blood pigment. With marked passive congestion these cells

became exceedingly numerous and frequently were desquamated into the alveolar spaces in sheets or long strands.

The pneumonic picture, both clinical and pathologic, lacks the usual direct and exudative evidence of bacterial involvement and, because of the hyperplastic cellular element, suggests an infection which is viral in origin. Descriptions by other investigators [1-7] of lungs in which influenza virus was associated with bacteria has shown a picture similar to that which we obtained in our cases in which there was also a concomitant bacterial infection. Our single case from which influenza virus A was obtained by culture from post-mortem lungs together with bacteria showed not only the two above-discussed characteristics of bacteria-free infection but also a small number of neutrophilic leukocytes.

Attempts to isolate influenza virus post mortem from human lungs with atypical pneumonias have been somewhat discouraging, as only one virus was obtained from 44 lungs. These results, however, are in accord with those of other investigators. Recently Maxwell *et al.*[8] succeeded in isolating influenza virus only four times from 37 specimens of lung and bronchus obtained at necropsy from patients with pneumonia, and not once from 50 cases with no pneumonia. It is interesting that in the few successful post-mortem cultures from lungs an associated bacterial infection was present also.

Histologic changes in the human lungs studied by us differ considerably from those experimentally produced by influenza virus in laboratory animals, especially mice.[9-13] The prominence of degenerative and necrotic changes in the bronchial epithelium is emphasized by all workers except McIntosh and Selbie [14,15] who noted thickening of the alveolar wall. In the rat the prominent pathologic alteration is the proliferation of the alveolar wall, rather than degenerative changes in the lining of bronchi, so that species difference may be important. One possible reason why experimental pneumonia of mice may differ histologically from the human disease is that, in the mouse, bacteria remain coincidentally with the virus, and these bacteria have not been eliminated by antibiotic therapy as in our human patients.

Summary

Lungs of children dying with pneumonia after receiving adequate antibiotic treatment contained few or no bacteria. These abacterial lungs showed extensive cellular hyperplasia of the alveolar walls and few or no neutrophilic leukocytes. The bronchi and bronchioles were free from involvement and appeared normal. It is suggested that the etiologic agent may be a virus.

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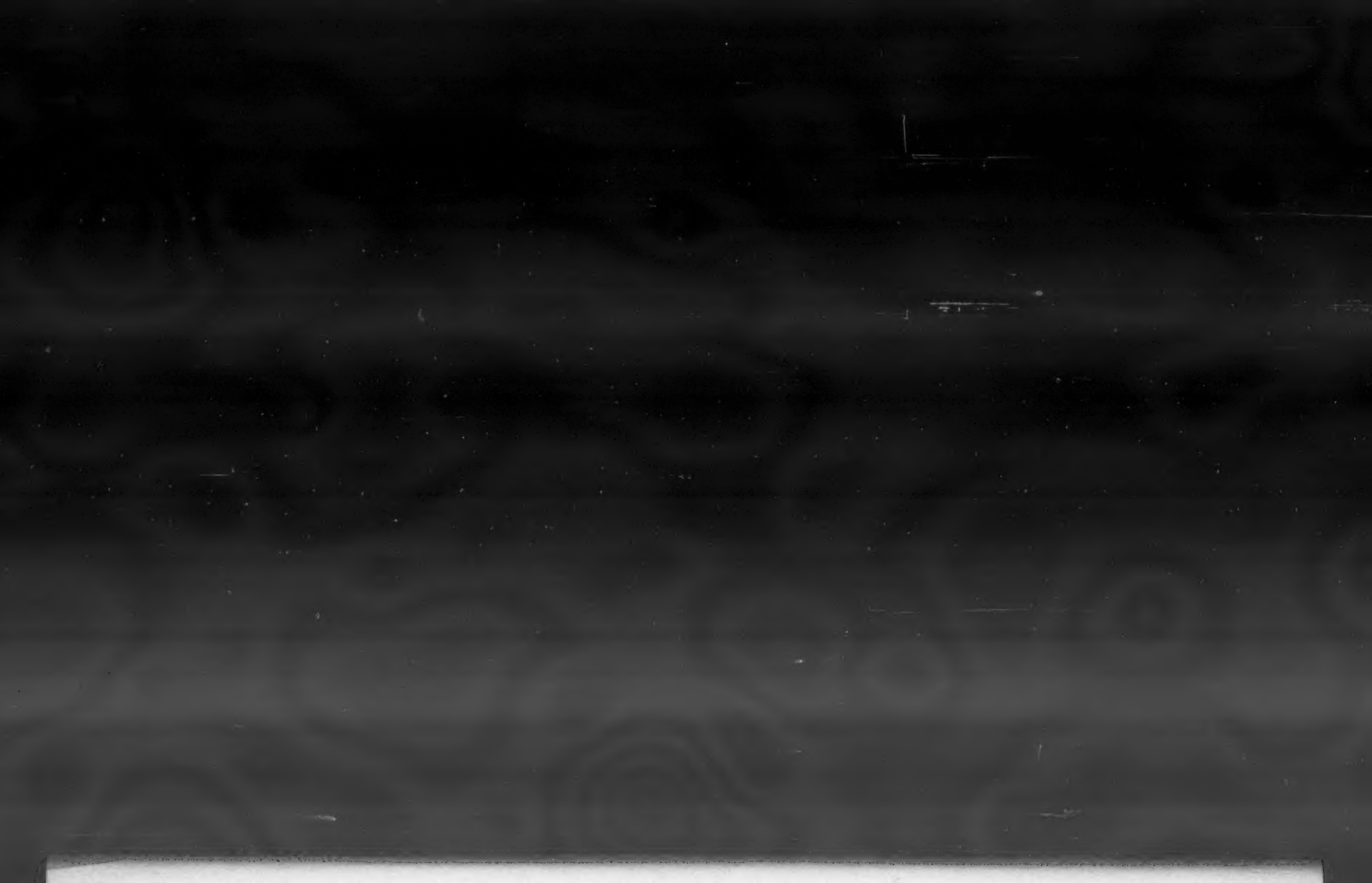
DESCRIPTION OF PLATES

PLATE 87

FIG. 1. Early hyperplasia of alveolar walls. × 120.

FIG. 2. Hyperplasia of alveolar wall. × 680.

FIG. 3. Extensive hyperplasia of alveolar wall with obliteration of alveoli. Respiratory ductules remain as open spaces. × 85.



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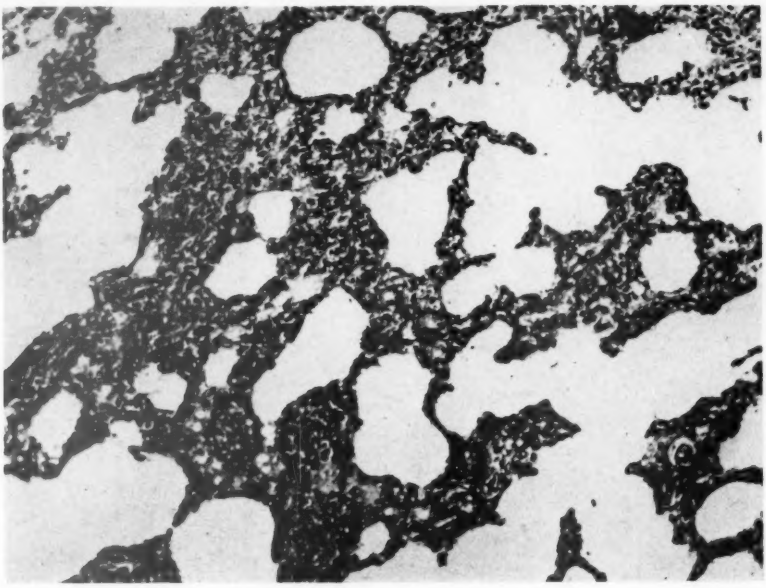

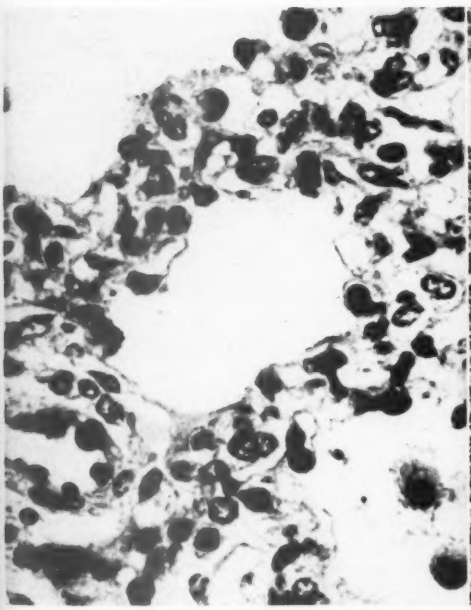

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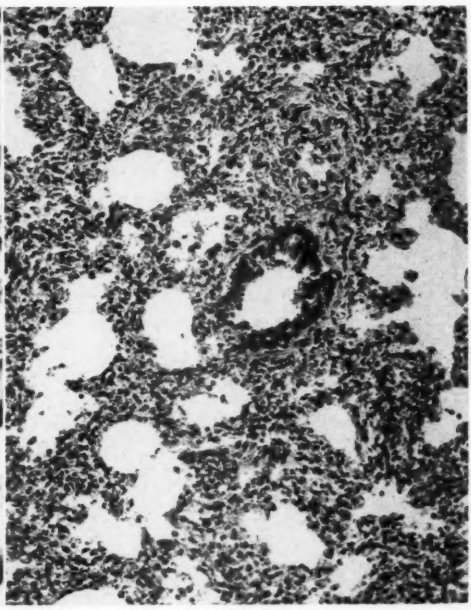


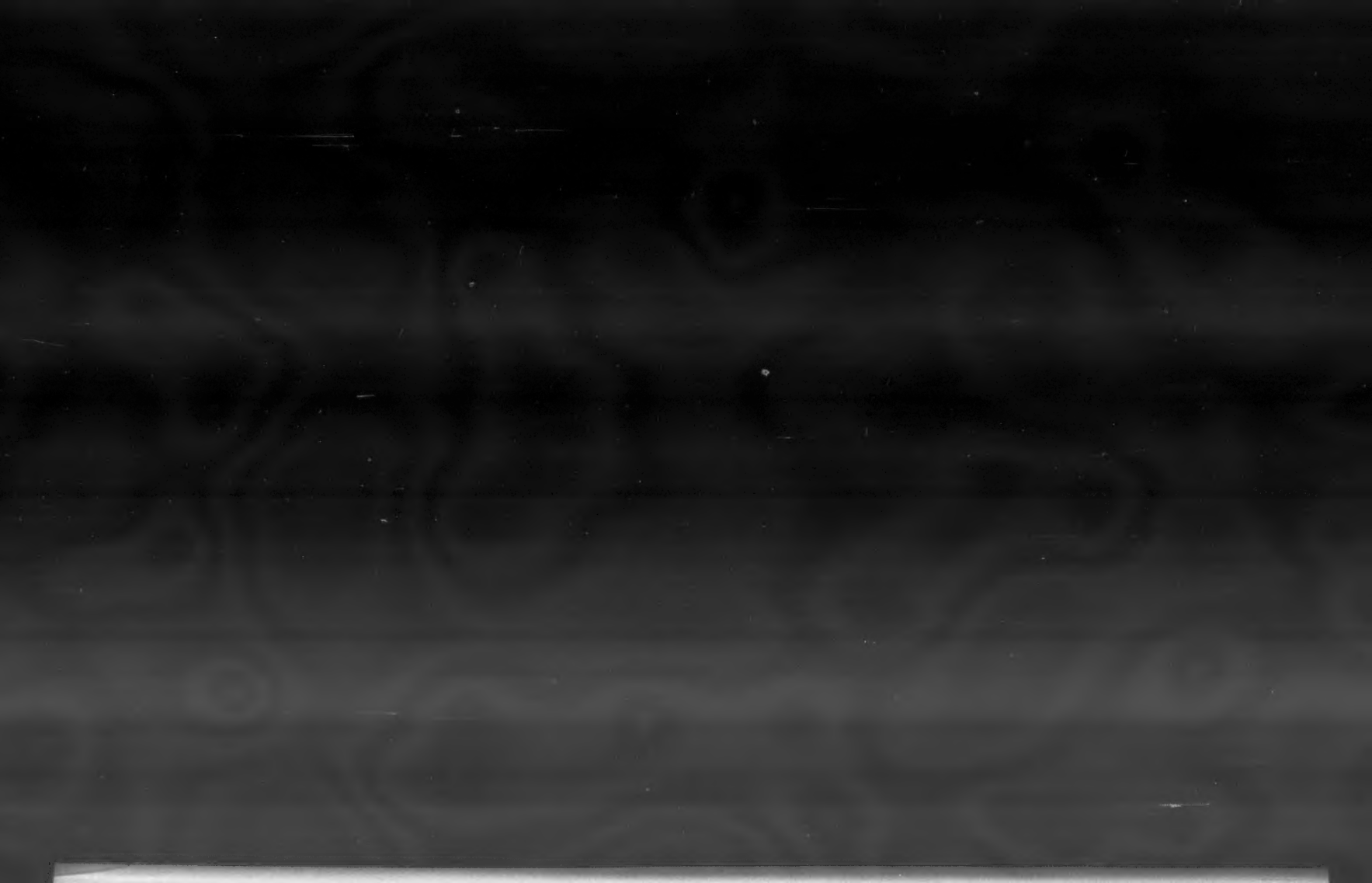
3

Menten and McCloskey Pneumonia in Children After Antibacterial Therapy

PLATE 88

FIG. 4. Extensive hyperplasia of alveolar wall with obliteration of alveoli. Respiratory ductules remain as open spaces. × 100.

FIG. 5. Exudation of serum and red blood cells into the alveoli. × 750.



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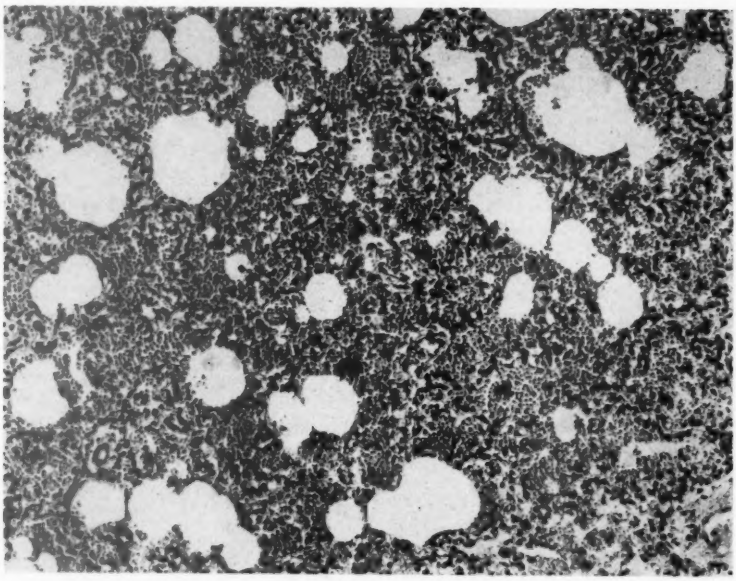

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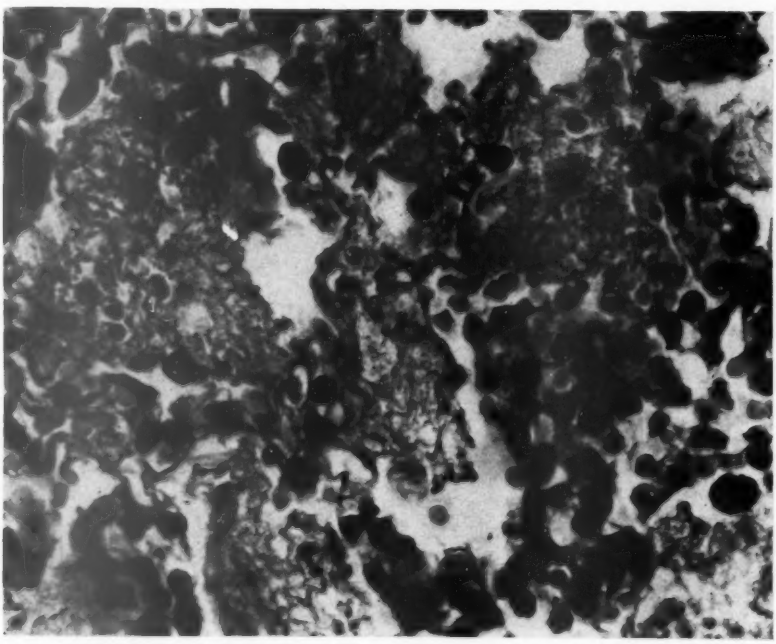


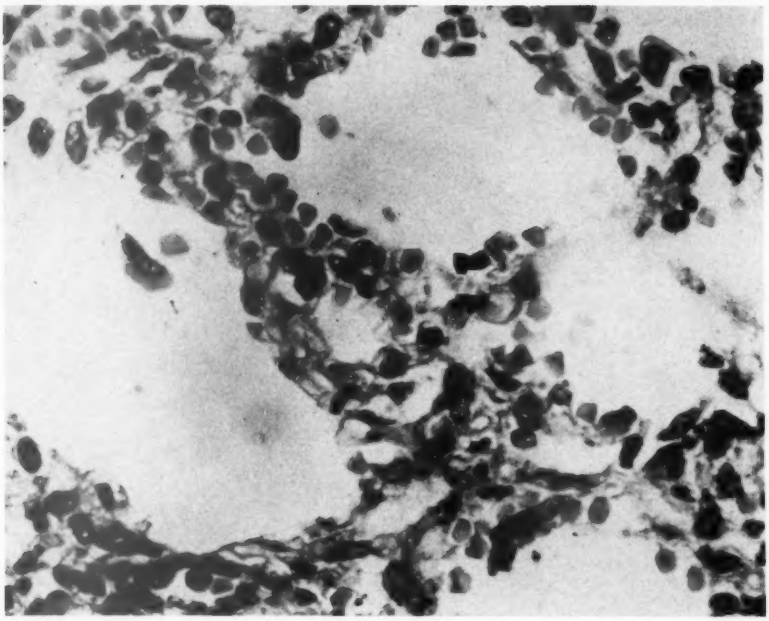
Menten and McCloskey Pneumonia in Children After Antibacterial Therapy

PLATE 89

FIG. 6. Exudation of serum and red blood cells into the alveoli. × 750.

FIG. 7. Heart lesion cells in alveoli and swelling of septal cells. × 750.

6



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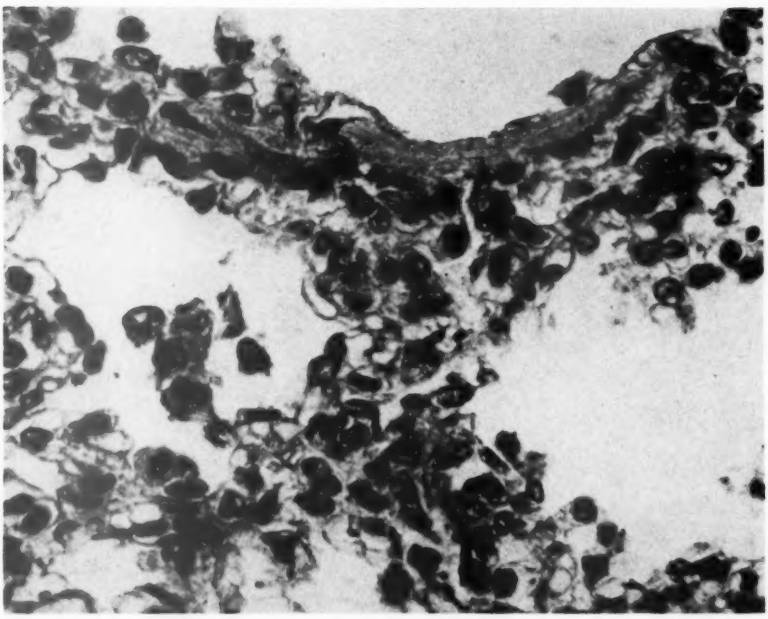


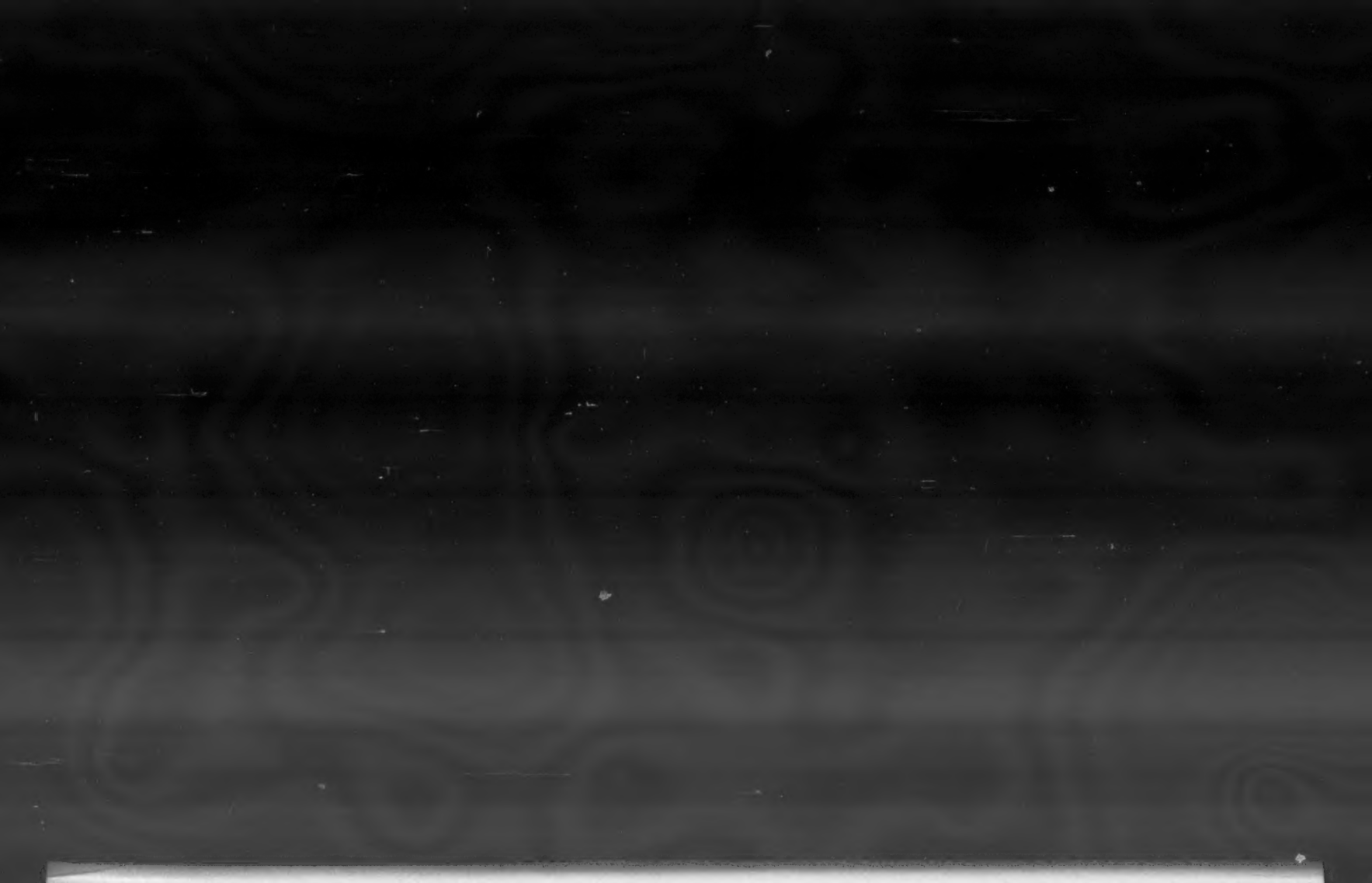
Menten and McCloskey Pneumonia in Children After Antibacterial Therapy

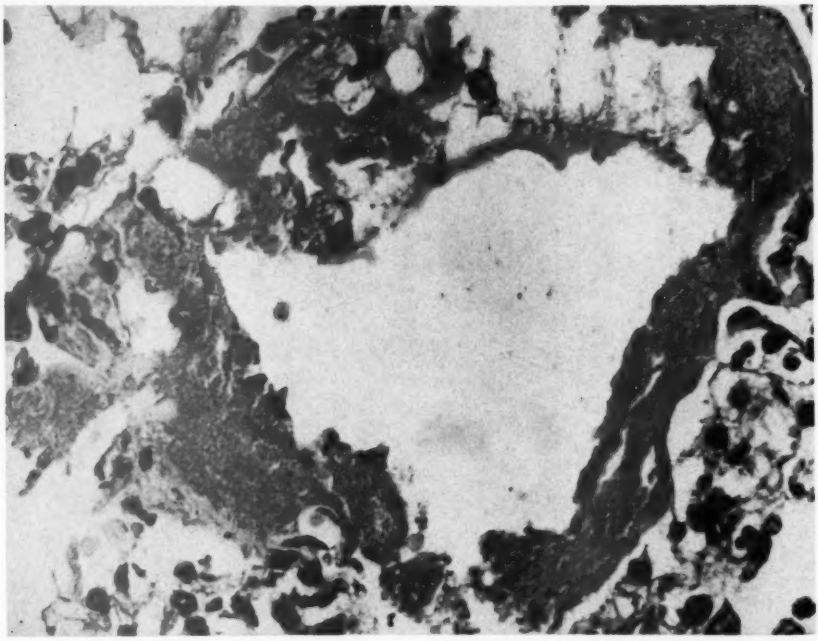
PLATE 90

FIG. 8. Hyaline membrane lining alveolar wall. × 750.

FIG. 9. Sheet of heart lesion cells in alveolus. × 900.

FIG. 10. Hyaline membrane bordering the lining of respiratory ductules. × 120.





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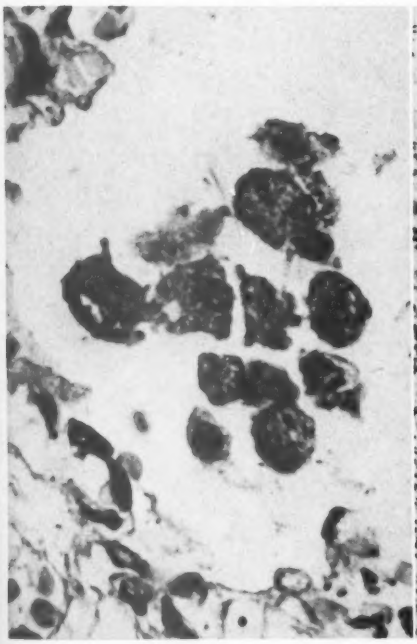

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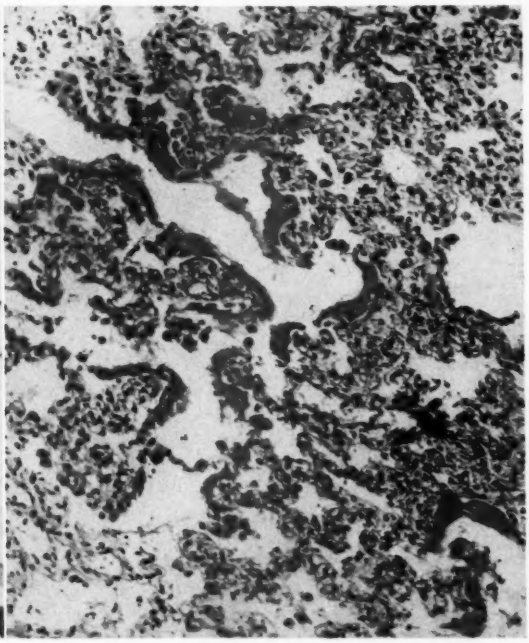

10

Menten and McCloskey

Pneumonia in Children After Antibacterial Therapy

LOCALIZED TUBERCULOID GRANULOMAS ASSOCIATED WITH CARCINOMA

Their Relationship to Sarcoidosis *

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Gherardi [1] recently reported a case of carcinoma of the bile ducts associated with what he described as Boeck's sarcoid in the regional lymph nodes. His paper has prompted the following discussion, based on 4 cases of carcinoma associated with lesions in the related lymph nodes resembling those of sarcoidosis and one case of an invasive bronchial "adenoma" in which similar tuberculoid lesions were present in the neighboring lung tissue. One case is of additional interest in that the carcinoma arose in the thyroid gland of a patient with Hashimoto's disease (struma lymphomatosa).

Gherardi's account [1] is the only record which it has been possible to find in which the coexistence of cancer and sarcoidosis has been claimed; the evidence upon which he based the latter diagnosis was wholly morphologic, and, for reasons to be given, it seems probable that the granulomatous process in his case was not a manifestation of sarcoidosis.

Report of Cases

Case 1

Carcinoma of Breast: Tuberculoid Granulomatous Axillary and Internal Mammary Lymphadenitis

E., a Jewish woman, born in 1900, was admitted to a hospital in March, 1949, complaining of a tender lump in the right breast, first noticed 4 weeks previously and slowly enlarging. There was no history of injury to either breast. The patient had never been pregnant. She gave no history of tuberculosis. Chronic, deforming polyarthritis in early adult life had long since ceased to show any activity. The family history was not relevant.

Clinical Examination. The patient was a small, thin woman, weighing 97 lbs. (44 kg.). The breasts were small and the nipples normal. A small, hard, mobile tumor was felt in the upper, outer quadrant of the right breast, and several smaller, ill defined, fairly firm nodules in the left breast. Several firm, mobile lymph nodes were present on the medial wall of the right axilla, the largest measuring 1 cm. across; no lymph nodes were palpable elsewhere. Examination revealed no abnormality in the respiratory, circulatory, and nervous systems or in the abdomen. Rectal examination was normal. There were old rheumatoid arthritic deformities of the wrists and hands. The skin was healthy. The salivary and lachrymal glands were normal. Except for banal refractive errors, there was no ocular defect. Chest radiographs were normal. The patient had no pyrexia while under observation.

Laboratory Investigations. Urinalyses were normal. Erythrocyte count was 5.04 millions per cmm.; hemoglobin, 92 per cent (Haldane), equivalent to 12.7 gm. per

* Received for publication, August 1, 1950.

100 cc.; leukocytes, 9,000 per cmm., with normal differential count. Erythrocyte sedimentation rate (Westergren) was 17 mm. in 1 hour. Chemical study of the blood serum gave the following results (figures per 100 cc.): Albumin, 4.8 gm.; globulin, 2.2 gm.; albumin-globulin ratio, 2.2:1; calcium, 10.8 mg.; inorganic phosphate, 3.4 mg. Serum Wassermann reaction and Kahn test were negative. Mantoux reaction (0.1 cc. of a 1:1000 dilution of old tuberculin) was positive.

On March 30, 1949, right-sided radical mastectomy was performed; during the operation a small lymph node was removed from beside the internal mammary vessels in the second right intercostal space. A routine radical postoperative course of deep roentgen therapy was given. When seen in July, 1950, the patient was in good general health and had gained 24 lbs. (11 kg.) in weight since the mastectomy; there was no clinical or radiologic evidence of recurrence.

Pathologic Findings * (Lab. No. C.813/49)

Breast. The breast was small and fibrous; there was an ill defined, hard tumor, 2 cm. in diameter, in its upper, outer quadrant. Microscopic examination showed much fibrosis of the breast, which contained little glandular tissue. There was moderate epithelial and myoepithelial hyperplasia, especially in the intralobular ducts, and several small, predominantly myo-epithelial, intraductal papillomas were present. Some ducts were moderately distended by retained secretion, which appeared granular and eosinophilic in the sections, with groups of spindle-shaped clefts, representing the site of lipoid crystals dissolved out during preparation of the material for imbedding in paraffin. The connective tissue around such ducts was moderately heavily infiltrated by lymphocytes and histiocytes, and there were small, focal lipogranulomas with scattered giant cells. The tumor was an intraductal and intra-acinar carcinoma, composed of large polyhedral cells; it had broken through the basement membrane to grow widely as an infiltrating scirrhous carcinoma. There was much central necrosis in the intraductal areas, and many large, foamy phagocytes had collected there. The stroma of the tumor was moderately heavily infiltrated by lymphocytes, with occasional small collections of histiocytes and scanty multinucleated "foreign body" cells in relation to small foci of inflammation of the adipose tissue and to degenerating areas of the neoplasm.

Axillary Lymph Nodes. Six firm nodes, 0.4 to 0.8 cm. in longest dimension, were found, the largest being nearest to the breast. Histologic examination showed numerous, sharply defined, tuberculoid foci in the largest node, particularly at one pole and adjacent to the hilus

* In all cases reported in this paper the specimens were fixed in formol-saline solution (4 per cent formaldehyde). Paraffin sections were stained by various methods. Material was not available for preparation of frozen sections.

(Fig. 1). These foci, which were seldom confluent, consisted of moderately large epithelioid histiocytes and occasional giant cells of the Langhans type, some of which were very large (Fig. 2); some giant cells contained "asteroid bodies," as many as seven being seen in one section in a single cell (Fig. 2), although usually they were solitary. The granulomatous foci had a scanty intercellular reticulin framework, and each was surrounded by a narrow capsule-like zone of reticulin. Some foci showed concentric, centripetal hyalinization. Irregular masses of homogeneous hyaline material, staining red with van Gieson's stain and blue with Mallory's connective tissue stain, were present in the lymphoid tissue surrounding the granulomas (Fig. 3) and appeared to have formed in relation to the reticulin framework of the node, partly replacing the argyrophilic fibers; similar material was found between the cells of some granulomatous foci. Plasma cells were scanty, and no more numerous in the areas of hyalinization than elsewhere in the medulla. There was no necrosis. No microorganisms were seen in sections stained by the Ziehl-Neelsen or Gram methods, or on examination of auramine preparations by fluorescence-microscopy. No involvement by carcinoma was found.

A few identical granulomas were found in one of the other five axillary nodes. No necrosis, hyalinization, organisms, or carcinoma was found in any of these nodes. They, and the non-granulomatous parts of the largest node, showed simple follicular and littoral-cell hyperplasia. Most of the follicles were small and consisted wholly of adult lymphocytes; a few were large and had large germinal centers in which evidence of phagocytic activity was minimal. The sinuses were slightly or moderately dilated; littoral-cell proliferation had filled their lumina with cells of strikingly epithelioid type (Fig. 4), in places with a resemblance to tuberculoid aggregations; the cells were all uninucleate. The changes in the sinuses were greatest at and near the hilus.

Internal Mammary Lymph Node. The specimen of internal mammary lymph node was a firm, spheroidal nodule, 0.3 cm. in diameter. Histologic examination showed that the normal structure was almost wholly replaced by dense, hyaline tissue, scattered through which, especially just within the fibrotic capsule, were small, more or less discrete aggregates of epithelioid cells with occasional Langhans' cells. No "asteroids" were seen. Most of these tuberculoid foci had undergone considerable hyaline sclerosis. There was no necrosis, and no organisms or carcinomatous deposits were found.

Case 2

Carcinoma of Breast: Tuberculoid Granulomatous Axillary Lymphadenitis with "Paramyloidosis" Following Intensive Radiotherapy

S., a housewife, born in 1886, was admitted in January, 1949, with a painless tumor in the right breast, first noticed 5 years previously in the upper, outer quadrant, whence it had slowly grown to occupy the whole breast. She had had no other illness, except glycosuria in 1926 during her only pregnancy, which terminated in stillbirth at full term.

Clinical Examination. The right breast was occupied by a hard, completely fixed tumor, continuous with a mass of hard lymph nodes in the right axilla. Enlarged, hard lymph nodes were present also in the right supraclavicular fossa. The left breast was normal. No abnormality was found in any other system. Radiographs of the chest were normal. Laboratory investigations revealed no hematologic or urinary abnormality. The Wassermann reaction was negative.

Treatment. Deep roentgen ray therapy was given to the cancerous breast and lymph nodes (total dose of 12,400 r. over six fields in 19 days). Radical mastectomy was performed on February 8, 1949, only 4 days after completion of irradiation; healing of the wound was surprisingly little delayed. During convalescence, persistent glycosuria led to investigation of the patient's glucose-tolerance; diabetes mellitus was diagnosed, and controlled on a daily dose of 12 units of ordinary insulin.

In January, 1950, a small tumor was found beside the nipple in the upper, outer quadrant of the left breast; no lymph nodes were palpable, and clinical examination otherwise was normal. Left-sided simple mastectomy was performed and followed by a course of deep roentgen ray therapy. Pathologic examination showed that the lesion was a scirrhous carcinoma, 2 cm. in diameter, composed of small polyhedral cells; no granulomatous lesions were found. In July, 1950, there was no evidence of recurrent or metastatic tumor or of other abnormality.

Pathologic Findings (Lab. No. C.347/49)

Right Breast. An ill defined, hard tumor occupied the entire center and the upper, outer quadrant of the breast, to the skin of which it was adherent. Microscopic examination showed that the growth was an intraductal, intra-acinar, and diffusely infiltrating carcinoma, composed of large polyhedral cells and largely of scirrhous type. There were marked changes due to x-irradiation in the tumor cells, stroma, and breast tissue, with small areas of fibrinoid necrosis in the latter. A few polymorphonuclear leukocytes, lymphocytes, and macrophages were scattered through the tissues; an occasional "foreign body" giant cell was present; no "asteroid bodies" were seen.

Axillary Lymph Nodes. Only three axillary lymph nodes were available for examination; the largest measured 1.6 by 0.6 by 0.5 cm. Histologic examination showed that the smallest node was almost completely replaced by polyhedral cell carcinoma with much fibrous stroma; no granulomatous tissue was seen in this node. In the second node there was carcinomatous permeation of part of the peripheral sinus, with extensive infiltration into the central part of the node and

little stroma formation. Two extensive areas of tuberculoid granulomatosis were present, one near the hilus and the other at one pole; the latter area was partly infiltrated by carcinoma (Fig. 5). The granulomas consisted of aggregates of loosely packed epithelioid histiocytes, with numerous multinucleated giant cells and occasional lymphocytes. The nuclei of the giant cells were situated peripherally; in the central cytoplasm there were irregular, pale areas, the larger of which each contained a well formed "asteroid" (Fig. 6), and the smaller ones a central globule of homogeneous, refractile material with the same appearance and staining reactions as the "asteroids." Some of the granulomatous foci were coalescent, but most were separated by a little fibrous tissue enclosing scanty lymphocytes. Each focus had a reticulin capsule and scanty reticulin fibrils between its component cells. There was no necrosis. Hyaline material surrounded some granulomas or was present nearby. The follicles of the surviving lymphoid tissue were small, and there was some dilatation of the sinuses with littoral-cell proliferation. Hemosiderin and hematoidin were present in moderate amount. The largest node showed very extensive replacement by carcinoma and granuloma. The neoplastic tissue was practically limited to one pole of the node, and consisted of large, bizarre cells, with a moderate degree of intercellular fibrosis; many cells were degenerate, and the appearances were those associated with heavy exposure to ionizing irradiation. The structure of the granulomatous foci was identical with that in the second node. Much homogeneous, eosinophilic material, resembling hyalin or amyloid, was present in the largest node in the interstitial tissue between the foci. Some of this material was stained yellow or yellow-pink by van Gieson's stain, although much of it took the usual brilliant red color of hyalinized connective tissue; similarly, some of it was colored purple by Mallory's connective tissue stain, in contrast with the blue of the rest of it and of the fibrous tissue generally. It did not stain metachromatically with methyl violet or other metachromatic stains for amyloid, but much of it showed affinity for Congo red to the same degree as a control section of an amyloid kidney, and this affinity was noticed also in the "asteroid bodies" in this case. No organisms were seen in Gram, Ziehl-Neelsen, or auramine preparations of each node.

Case 3

Carcinoma of Thyroid Gland Complicating Hashimoto's Disease: Tuberculoid Granulomatous Inflammation of a Regional Lymph Node

J., a widow, born in 1889, was admitted in April, 1949, because of a steadily enlarging goiter, first noticed 6 months previously as a firm swelling in the midline of

the neck. Some interference with swallowing had developed. She gave a history of lethargy, dryness of the skin, thinning of the hair, and marked intolerance of cold: these symptoms had been present for some years prior to the appearance of the goiter.

She showed the stigmata of a moderate degree of myxedema. Her facies was of hypothyroid type, and her skin myxedematous. She had lost a considerable amount of hair from the scalp, the lateral parts of her eyebrows were hairless, and body hair was scanty. Her tongue was slightly enlarged. The thyroid gland was moderately enlarged and hard, particularly its right lobe and isthmus. Several firm, mobile lymph nodes could be felt beside the lower pole of the left lobe. The pulse was regular, and its basal rate was 60 per minute. The arterial blood pressure was 130/90 mm. of Hg. Clinical examination otherwise revealed nothing noteworthy. Radiographs showed compression of the upper end of the trachea and esophagus by the enlarged thyroid gland; slight enlargement of the cardiac shadow was demonstrated radiologically, but no other abnormality was seen in the chest. The oral temperature varied between 97.0° and 97.8° F. (36.1° and 36.6° C.). The basal metabolic rate was minus 18 per cent. The serum Wassermann reaction was negative. A trace of albumin was found in the urine.

The clinical diagnosis was thyroid carcinoma. Total thyroidectomy was performed on April 11, 1949. The entire right lobe, isthmus, and part of the left lobe appeared to be replaced by neoplastic tissue, which was partly friable and partly hard. With the exception of the posterior surface of the left lobe, the entire gland was firmly adherent to the adjacent structures, from which it could be separated only by sharp dissection. Three small, firm masses of tissue, not continuous with the thyroid, and thought to be lymph nodes involved by carcinoma, were removed from beside the left inferior thyroid artery.

Despite postoperative deep roentgen ray therapy, local recurrence developed and rapidly grew to a large size; there was no evidence of tumor elsewhere in the body. The patient died at home 11 weeks after the thyroidectomy. There was no necropsy.

Pathologic Findings (Lab. No. B.657/49)

Thyroid Gland. No macroscopic description of the specimen of thyroid gland is available. Most of the sections showed complete replacement of thyroid tissue by a very cellular, partly necrotic neoplasm (Fig. 7), composed mainly of rounded, ovoid, or small spindle-shaped cells, with little stroma. The tumor cells were hyperchromatic, and most of them had little cytoplasm; the round cells varied in size, but were at least half as large again as lymphocytes; the nuclei stained deeply and uniformly, and their outlines were indistinct. For the most part there was no structural pattern in the tumor, but in places it had a trabecular structure and in these areas many of its cells were large and had a wide rim of clear or finely reticulated cytoplasm (Fig. 8). In a few areas imperfectly formed acini had been differentiated. The growth infiltrated deeply into skeletal muscle, the fibers of which were widely separated and showed a varied degree of degeneration. In some areas, where adipose tissue was involved, necrosis of the neoplastic tissue was accompanied by fat necrosis with foci of lipogranulomatous reaction.

Only occasional thyroid lobules were found in sections of the right lobe, and these were without exception at the periphery of the gland; the thyroid capsule and trabeculae in these areas were thickened and hyaline; the lobules consisted of groups of small acini, with the scanty stroma between them infiltrated by typical mature lymphocytes. The acini were lined by large, pale, cuboidal epithelial cells. Little colloid was present; some of it was peculiarly dense, refractile, and deeply staining. Large, multinucleated, symplasmic masses, resembling "foreign body" giant cells, were present in some acini, often moulded around the dense colloid. Similar cells and many mononuclear histiocytes were present where the neoplasm invaded and destroyed the deeper lobules, in places forming tuberculoid foci (Fig. 9).

Sections of the isthmus and left lobe showed similar changes. In addition, however, there were extensive areas not involved by carcinoma, and here the appearances were characteristic of Hashimoto's disease (Fig. 10): the acini were small and lined by large, pale cuboidal cells, and the interacinar stroma was heavily and diffusely infiltrated by typical mature lymphocytes, with many medium-sized to large lymphoid follicles with large germinal centers.

Cervical "Lymph Nodes." Of the three structures thought at operation to be lymph nodes, two consisted wholly of anaplastic carcinoma reproducing the various features seen in the main growth, with no lymphoid tissue recognizable. The third structure was a lymph node, throughout which there were closely packed, discrete or confluent tuberculoid granulomas; only two small deposits of carcinoma were found, both of clear cell, trabecular type. The appearances of the granulomatous foci and of the remaining lymphoid tissue differed in no way from those in case 1. No microorganisms were found.

Case 4

Carcinoma of Bronchus: Tuberculoid Granulomas and Giant-Celled Sinus Histiocytosis in a Regional Lymph Node

A., a male, born in 1925, served in Britain as an Army physical training instructor from 1941 until he was demobilized in 1947: at that time his weight was steady at 163 lbs. (74 kg.) and he was in excellent health. In 1947 he developed quinsy, followed by right-sided dry pleurisy; the latter recurred in the spring of 1948. For 14 days in November, 1948, he noticed slight blood-streaking of his sputum in the mornings, and during that period he again had pleuritic pain in the right side; chest radiography was normal. In December, 1948, he began to develop slowly progressive stiffness, then weakness, of both legs, which spread to the trunk and later (April, 1949) affected his speech and facial musculature. Neurologic examination in May, 1949, revealed a classical picture of myasthenia gravis, and his symptoms responded dramatically to treatment with prostigmin. He had no goiter, and his basal metabolic rate was plus 2 per cent. Radiographic examination of the chest showed no thymic

enlargement, but an area of collapse in the upper part of the lower lobe of the right lung was seen. No abnormality was seen on bronchoscopy. Tomographic examination showed an irregular shadow in relation to the main bronchus of the right lower lobe. He was losing weight rapidly, and exploratory thoracotomy was advised. Clinical examination of his respiratory and circulatory systems and abdomen showed no abnormal signs.

Laboratory Investigations. Urinalyses were normal. Blood counts showed erythrocytes, 6.64 millions per cmm.; hemoglobin, 130 per cent (Haldane), equivalent to 18.0 gm. per 100 cc.; leukocytes, 8,700 per cmm.; polymorphonuclear neutrophils, 74 per cent (6,438); eosinophils, 3 per cent (261); lymphocytes, 15.5 per cent (1,348); monocytes, 7.5 per cent (652). Erythrocyte sedimentation rate (Westergren), 1 mm. in 1 hour. Serum Wassermann reaction was repeatedly negative. Sputum was examined repeatedly for *Mycobacterium tuberculosis* during a period of several weeks before operation. Results were negative persistently until a very small number of acid-alcohol-fast bacilli was found in the last of three consecutive daily specimens sent for examination in the week preceding operation; the pathogenicity of the organisms was not investigated, nor was the sputum examined by cultural methods. The Mantoux reaction (0.1 cc. of 1:1000 and 1:100 O.T.) was negative.

Thoracotomy and right pneumonectomy were performed on July 19, 1949. Despite mechanical respiration and large doses of prostigmin, the patient died of respiratory failure within 24 hours of the operation.

Pathologic Findings

Surgical Specimens (No. C.1873/49). Right Lung. In the right lung, a grayish white, partly necrotic tumor surrounded the lower lobe bronchus near its origin, protruding into the lumen and extending also to a depth of 4 cm. into the body of the lobe. There was considerable collapse of the lower lobe, with some retention of tenacious mucus in the bronchi peripheral to the neoplasm. No abnormality of the other lobes was seen. No lymph nodes were found in the specimen. Microscopic examination showed that the tumor was a bronchial carcinoma of the "large-oat-cell" type, with areas of squamous cell structure. No granulomatous lesions were found in the tumor or in the lung tissue.

Lymph Node Excised from Below the Azygos Vein. An anthracotic lymph node, excised from below the azygos vein, was spheroidal, 1.1 cm. in diameter. Sections showed that the peripheral sinus was infiltrated in one small area by undifferentiated neoplastic cells. There was a moderate degree of simple reactive hyperplasia of the lymphoid follicles, but the most striking changes were those in the sinuses. There was a considerable degree of littoral-cell proliferation, of patchy distribution and affecting predominantly the peripheral sinus and the adjacent parts of the radial sinuses. The littoral-cell proliferation mainly took the form of an increased number of rounded histiocytes lying free in the lumina of the sinuses, but in places the cells were of epithelioid type, with, however, a considerable proportion of large, round, binucleated or multinucleated forms, which here and there had

infiltrated the adjacent medulla (Fig. 11). An occasional large cell contained a small but typical asteroid. In a few places the epithelioid and multinucleated cells were grouped to form definite tuberculoid aggregates (Fig. 12), some of which showed early concentric hyalinization. Fine reticulin fibers were present between the cells of these aggregates. No necrosis was present. No organisms were found despite prolonged search of Ziehl-Neelsen and auramine preparations.

Summary of Necropsy (EN 206/49). The body, that of a greatly emaciated young man, weighed 97 lbs. (44 kg.). There was a fresh, right-sided thoracotomy wound. The pneumonectomy site showed no unusual features; a hemohydropneumothorax (800 cc. of fluid) was present on the operation side, and there was slight surgical emphysema of the anterior mediastinum. The trachea contained much tenacious mucus; the lower lobe of the left lung was collapsed and its bronchi filled with mucus. The thymus gland was small and almost completely fatty; it weighed 15 gm. The other thoracic organs were normal, as were the cranial, cervical, abdominal, and pelvic viscera and the external genitalia. The accessible parts of the skeleton were normal. No neoplastic tissue or tuberculous lesions were found, and there was no apparent lymphadenopathy. *Post-mortem Histologic Findings.* No evidence of neoplasia or of tuberculosis or other granulomatous process was found in any part. The thymus showed marked fatty replacement but no other noteworthy features. No abnormality of the central nervous system, peripheral nerves, or skeletal muscles was found.

Case 5

Invasive Bronchial "Adenoma": Tuberculoid Granulomas in Interstitial Pulmonary Lymphoid Tissue

S., a woman, born in 1915, had had repeated attacks of left-sided dry pleurisy since 1945. No radiologic abnormality was found until 1947, when a small opacity was discovered near the root of the upper lobe of the left lung; this remained unaltered on periodical re-examination, until, in March, 1949, it was found to be slowly enlarging, with concomitant development of partial collapse of the lobe. Bronchoscopic examinations showed no abnormality. Bronchography was not performed at any time, nor did the patient receive any oily medicaments. Apart from the bronchopulmonary lesion there was no clinical evidence of any abnormality. No acid-alcohol-fast organisms were found in the sputum. The Mantoux reaction (0.1 cc. of 1:1000 and 1:100 O.T.) was negative.

Left upper pulmonary lobectomy was performed in June, 1949. When seen in July, 1950, the patient was in excellent health.

Pathologic Findings (Lab. No. C.1491/49)

The specimen was the upper lobe of a left lung. A sharply outlined, firm, white tumor obstructed the main bronchus of the lobe and ex-

tended into the adjacent lung tissue; the tumor, which was roughly spherical, measured 4.4 cm. in diameter. The lung tissue was collapsed, and there was considerable fibrosis; the bronchi peripheral to the obstruction were moderately dilated and contained a little thick, mucopurulent exudate. No lymph nodes were included in the specimen. Microscopic examination showed that the tumor was a characteristic, trabecular and pseudo-acinar, small-cell bronchial "adenoma," surrounded by a thick hyaline capsule. The capsule was infiltrated and, in places, penetrated by tumor cells. Sections of the rest of the lobe showed considerable collapse, with interstitial fibrosis. Bronchiectasis and bronchiolectasis were associated with heavy lymphocytic and plasma cell infiltration of the surrounding tissues, in which there were numerous large lymphoid follicles with well developed germinal centers. Small areas of non-specific ulceration were present in the bronchi. "Foamy" macrophages were fairly numerous in the alveoli and were sparsely present in the peribronchial interstitium, where occasional multinucleated cells of "foreign body" type also were seen. Small tuberculoid foci were present in the lymphoid tissue alongside the interlobular septa, often situated beside or encroaching upon the germinal centers (Fig. 13). These foci were composed of epithelioid cells and giant cells. The latter had abundant cytoplasm but few nuclei, which were arranged either peripherally or distributed more uniformly throughout the cell. Very occasionally a small, well formed "asteroid body" was present in one of the giant cells. Various stages in the development of the granulomatous foci could be seen, from small, discrete collections of histiocytes, some of which had the foamlike cytoplasm of lipophages, through larger aggregates showing epithelioid metamorphosis of the histiocytes, and on to pseudotubercle formation. The tuberculoid lesions had a delicate framework of reticulin; there was no fibrosis or hyalinization. Necrosis was not found in any of the lesions, and organisms were not seen in Ziehl-Neelsen or auramine preparations.

Discussion

The simultaneous presence of granulomatous inflammation and neoplasia, whether in different parts of the body or in close topographic relationship, is quite common. The association is usually a chance one, explicable by the comparative frequency of each of these two distinct pathologic processes. It is within the scope of this paper to discuss their coexistence only in the limited context of association of the two processes in the same region of the body, either in one organ or in an organ and its regional lymph nodes. This association may be coincidental, the two conditions arising independently in the same area,

either simultaneously or at different times; alternatively, the development of either process may be dependent upon the presence of the other. As it is impossible in many cases to determine whether the association is coincidental or not, it is more convenient to discuss such coexistent lesions according to the nature of the granulomatogenic agent at work in each case, rather than to consider them primarily on the basis of their possible etiologic interrelationship.

Granulomas Caused by Products of Neoplastic Growth. The best known example of granuloma of the type caused by products of neoplastic growth is probably that which develops around keratinic débris and lipid degeneration products in the stroma of some keratinizing squamous carcinomas. In this case the inflammatory reaction appears to be essentially the same as that developing in relation to ruptured or infected epidermoid or sebaceous cysts and in the stroma of the related "benign calcifying epitheliomas" of the skin (Malherbe-Chenantais lesions).[2] A similar granulomatous reaction sometimes is seen in lymph nodes draining lesions of these types; this is true particularly in nodes which are the seat of metastases of keratinizing carcinomas, but it occurs also in the absence of neoplastic involvement, in which case the inflammatory reaction appears to be the result of absorption of irritant material from the site of the initial lesion. Morphologically, this reaction most commonly takes the form of a simple histiocytosis, with formation of some "foreign body" giant cells; occasionally, however, more or less well formed tuberculoid follicles develop.

Tuberculoid lesions, formed of congeries of epithelioid cells with occasional multinucleated giant cells, are seen in certain other neoplasms, in which their significance is obscure; such foci are most often seen in dysgerminomas [3] but they are occasionally found in seminomas, and a similar observation was recorded by Hartz and van der Sar [4] in a retroperitoneal tumor which they described as a neurocytoma. In such cases tuberculoid lesions appear not to have been seen in the lymph nodes in the absence of metastatic tumor deposits there. It has been suggested that lipids are the causative factor of the granulomatous foci in these neoplasms.[4]

Granulomas Caused by Agents of Extraneous Origin. The presence at the site of a carcinoma or other neoplasm of a granuloma caused by a recognizable animate or inanimate agent unrelated to the neoplasm has been observed repeatedly. Some aspects of such an association of carcinoma and tuberculosis were reviewed by Randall and Spalding,[5] with particular reference to its occurrence in the ileocecal region and large intestine; also the regional lymph nodes in such cases may be affected by one or both of these disease processes. Sometimes carci-

noma may coexist with syphilitic gummas, leprotic or mycotic lesions, or other infective granulomas in the same site. A granulomatous reaction to the presence of non-living irritants may occur by chance in the same situation as a neoplasm, *e.g.*, "corpus amylaceum" granulomas coexisting with carcinoma in the prostate gland, and talc granulomatosis of the pelvic peritoneum associated with carcinomatous deposits in the same area (personal observations). A similar association may be seen when neoplastic deposits develop in laparotomy scars, in which, following previous surgical measures, granulomas have formed in relation to talc crystals or lycopodial spores from dusting powders, to insoluble, crystalline derivatives of drugs, including sulfonamides, or to suture material (personal observations).

In exceptional instances a pre-existing granuloma appears unequivocally to have been the starting-point for neoplastic growth, *e.g.*, the occasional development of carcinoma in long-standing lesions of lupus vulgaris. Sometimes, as in the case of some cancers of the alimentary tract, the ulcerated surface of a neoplasm appears to provide a suitable soil for colonization by granulomatogenic microorganisms, particularly *Mycobacterium tuberculosis*.[5] Food remnants deposited in craters or fissures in the surface of carcinoma of the alimentary tract may cause a local foreign body granuloma, and I have seen the development in comparable fashion of an oleogranuloma at the site of an ulcerated carcinoma to which dressings had been applied which were impregnated with a medicated paste the basis of which was liquid petrolatum. Similarly, in a case reported by Klee,[6] a characteristic oxyuris granuloma resulted from penetration of a gravid threadworm into the tissues at the site of a carcinoma of the uterine cervix; Klee considered that the irregular surface of the growth had predisposed to invasion by the worm.

Innumerable other examples of the intimate association of granulomas and neoplasms could be listed. It is not necessary to discuss further those granulomatous lesions the direct excitant of which is a known living or inanimate agent. The coexistence of sarcoidosis (Besnier-Boeck-Schaumann disease) and neoplasia, however, remains to be considered.

Sarcoidosis and Neoplasia. Search of the literature has revealed no unequivocal record of coexistent sarcoidosis and malignant neoplasia. This may be explained in part by the different age periods in which the two processes have their greatest incidence. Leitner [7] gave the maximum age incidence of sarcoidosis as being between 20 and 40 years, well below the age period of the greatest incidence of cancer.

Gherardi [1] appears to be the only author who has claimed to have observed the association of these diseases. His case was that of a woman, 61 years old, with obstructive jaundice; a lymph node, removed at laparotomy from beside the upper end of the common bile duct, showed changes which were interpreted as those of sarcoidosis. The patient died a few months later. Necropsy revealed a scirrhous adenocarcinoma arising in and obstructing the common hepatic duct. There were several greenish cysts in the tumor; they measured up to 0.2 cm. in diameter and were filled with eosinophilic material and cell débris. The liver showed biliary cirrhosis. The gallbladder was small and its wall slightly thickened; its lumen was filled by a semisolid cast of dark green-brown, somewhat stringy material which was slightly adherent to the wall. Histologic examination showed that the gallbladder wall was moderately fibrotic; slight lymphocytic infiltration and a few multinucleated giant cells were seen, and there was a moderate amount of intracellular brown pigment. The lymph nodes at the upper margin of the pancreas and between it and the porta hepatis were enlarged, discrete, gray-green, and rubbery; the largest node measured 4 by 3 by 1 cm., and lay beside the junction of the cystic and common hepatic ducts. Microscopically, the normal structure of these nodes was largely obscured by an inflammatory process consisting of many small, discrete, or slightly confluent granulomas of fairly uniform size. The granulomas consisted of epithelioid cells, with a few lymphocytes and occasional Langhans' giant cells; some showed more or less centripetal replacement by hyaline fibrous tissue, and in some nodes sclerosis had obliterated all structure except for a few granulomatous foci. Metastatic carcinoma was present in one node. The sinuses of the nodes contained many large mononuclear cells, some filled with brown pigment in which there was no demonstrable iron. The spleen, which weighed 300 gm., showed some fibrosis of the pulp and slight atrophy of the malpighian corpuscles. Examination of the other abdominal organs appears not to have revealed any granulomatous lesions. As the necropsy was limited to examination through an abdominal incision, the thoracic viscera were examined only by inspection and palpation *in situ;* no gross abnormalities were found. No superficial lymph nodes were palpable.

Gherardi [1] interpreted the lymph node changes as representing "Boeck's sarcoid." He felt that the association of this condition with carcinoma in the same area was not likely to be fortuitous, particularly in view of the tendency to fibrosis common to both processes. He suggested, very tentatively, that their coexistence might have resulted

from "an expression of 'regional weakness' or 'terrain sarcoidique'" present before either condition developed, or from induction, by whichever disease occurred first, of a local predisposition to development of the other. From the marked fibrosis present both in the carcinoma and in the "sarcoid" lesions he concluded that "It may be that Boeck's sarcoid is a type of tissue response indicating resistance of the body: in this case, resistance to carcinoma."

Gherardi's [1] diagnosis of sarcoidosis appears to be open to question. A diagnosis of sarcoidosis can properly be reached only by study of the patient's case as a whole, analyzing and correlating the history, the clinical findings, the results of exhaustive radiologic, biochemical, bacteriologic, and immunologic investigations, and the histologic findings in biopsy material. Histologic findings alone are not adequate to justify making a diagnosis of sarcoidosis; the most that may safely be said on histologic grounds in any case is that the appearances are consistent with the presence of that disease. In Gherardi's case the histologic appearances themselves seem to have been atypical, in so far as can be judged from the photomicrograph illustrating the lymph node changes (Figure 2 of his paper [1]). The tuberculoid foci shown in the photograph differ in several features from those usually seen in sarcoidosis: they are poorly demarcated from the surrounding lymphoid tissue, their component cells are loosely packed, and throughout the foci there is a marked infiltration by lymphocytoid cells. A further point against the diagnosis in this case is the quite uncharacteristic localization of the lymphadenopathy to a single group of lymph nodes: although the lesions of sarcoidosis may be clinically manifest predominantly in one part of the body, the disease is essentially a generalized affection. In the case under discussion, however, no other lesions suggestive of sarcoidosis were found at necropsy, and there appears to have been no ante-mortem evidence in corroboration of the histologic diagnosis. Other explanations of the nature of the lymphadenopathy in this case must be sought. Scirrhous metastatic carcinoma can reasonably be considered to be excluded by Gherardi's description; similarly, in view of the absence of other evidence of infection it seems unlikely that the lymph node changes were a manifestation of one of the specific infective granulomatoses. There remains the possibility that the lymphadenopathy was the direct expression of the granulomatogenic action of irritant substances, possibly lipoidal, formed in bile stagnant within the gallbladder and possibly in the cystic areas of the neoplasm. While no comparable reaction appears to have occurred in the cirrhotic liver, it is noteworthy that multinucleated giant cells

were present in the wall of the gallbladder, which contained an adherent cast of inspissated bile; it may be significant that the largest lymph node was found in the immediate vicinity of the junction between the cystic and common hepatic ducts. Intracellular pigment, apparently biliary, was present in the wall of the gallbladder and also in macrophages in the sinuses of the affected lymph nodes; the generalized icterus makes the significance of the latter observation equivocal: the necropsy report does not make it clear that the nodes were more intensely jaundiced than other tissues, but the impression given is that such was the case. It must be remarked that the escape of bile into the tissues, *e.g.*, in the liver in cases of obstructive jaundice, does not ordinarily lead to development of a tuberculoid reaction: at most, retained bile may become so inspissated that it acts apparently as a foreign body, around which multinucleated giant cells form in the attempt to dispose of it. Nevertheless, the action of some irritant produced in consequence of the biliary obstruction seems to offer the most likely explanation of the granulomatous lymphadenitis in Gherardi's case.

Comparable tuberculoid granulomas are found very occasionally in the axillary lymph nodes in cases in which escape of altered secretion from obstructed mammary ductules has evoked a lipogranulomatous reaction in the breast tissue. Similarly, in certain cases of thyroiditis of the Riedel-de Quervain type, I have seen small granulomatous foci in the regional lymph nodes which are similar to the pseudotubercles in the affected thyroid gland. Such observations show that in cases in which a granulomatous reaction occurs in the tissues of an organ, due to the presence in the interstitium of some irritant of local origin, similar granulomas may occur in the lymph nodes draining the area, presumably due to absorption of the granulomatogenic material and its transportation in the lymph.

Discussion of the Cases Reported

The 5 cases reported in this paper share a common feature: the simultaneous presence in one area of an epithelial neoplasm and of involvement of part of the regional lymphoid tissue by a tuberculoid granulomatous process. The granulomas were structurally similar in all of the cases, being composed of epithelioid histiocytes and small or large multinucleated cells. Most of the giant cells were of the Langhans type, with multiple peripheral nuclei (3 to 50 in one plane) and a finely granular, eosinophilic cytoplasm, which was less dense at the center of the cell; only a few giant cells were of the so-called foreign

body type, with nuclei distributed throughout the cell. In the different cases the foci varied in compactness and cellularity, in the proportion of giant cells, and in the degree of lymphocytic infiltration, which was never great. Most of the granulomas were discrete: only where the foci were closely packed was there any coalescence. Each focus was enclosed by a narrow, capsule-like zone of reticulin; a few reticulin fibrils also lay between the component cells. In all but the fifth case there was some hyaline sclerosis of a proportion of the foci, most marked in their peripheral parts. None of the granulomatous tissue was necrotic. No microorganisms were seen.

In the first 4 cases the granulomatous process affected lymph nodes draining a carcinomatous area. In case 1, tuberculoid foci were most numerous in the largest axillary node, which was the one nearest the cancerous breast; four of the remaining five axillary nodes were not involved. There was extensive granulomatous involvement and hyalinization of the small internal mammary node. In case 2, two of the three axillary nodes examined were involved, one of them extensively. In case 3, there was widespread involvement of the only lymph node identifiable, and in case 4 only the involved node was available. Except in case 3, the foci were not uniformly distributed throughout the affected nodes but were most numerous near the hilus. They appeared in each case to have developed in the sinuses, which elsewhere showed more or less well marked littoral-cell proliferation and histiocytosis, epithelioid metamorphosis, and all stages of tuberculoid aggregation. In case 4, in which the tuberculoid foci were fewest in number, the earlier changes in the sinuses corresponded in places with those occasionally seen as a simple reactive phenomenon in the lymph nodes of children, and described by Robb-Smith [8] as giant cell sinus reticulosis. In the specimen in case 5, the relevant changes were limited to the intrapulmonary lymphoid follicles: in the affected follicles all stages in development of the granulomas were found, from small collections of histiocytes, some of which had the structure of lipophages, up to well formed tuberculoid foci.

Apart from demonstration of tuberculin sensitivity in case 1, no clinical or radiologic evidence of tuberculosis was found in any of the 5 cases. The Mantoux reaction was negative with a test dose of 1.0 mg. of old tuberculin in cases 4 and 5, and was not investigated in cases 2 and 3. In case 4, acid-alcohol-fast bacilli were found on a single occasion, in the last of many specimens of sputum examined prior to the pneumonectomy: the bacilli were very scanty, and no tuberculous lesions were found in the excised lung, which was particularly care-

fully searched for an early primary focus, or at necropsy. In these circumstances the findings in the sputum must be considered to be of doubtful significance.

In none of the cases was there any sign of lymphadenopathy other than in the surgical specimens, and no splenomegaly, hepatomegaly, skin lesions, or other abnormality suggestive of sarcoidosis or of any other generalized disorder of the lympho-reticular system was found. It seems highly improbable that there was any relationship between the localized lymphadenopathy and the history of rheumatoid arthritis in case 1, or between the lymphadenopathy and the presence of mild diabetes mellitus in case 2.

In view of the regional localization of the lesions in the lymphoid tissue, and, in the case of the affected lymph nodes, of their development in relation to the sinuses, it seems likely that they represent a reaction to irritant material, probably of lipoidal or lipoprotein nature, produced in the tissues drained by the affected lymphoid tissue. Ductal papillomatosis in the carcinomatous breast in case 1 was associated with a lipogranulomatoid reaction to retention of secretion in the ducts and also in relation to small inflammatory and degenerative foci in the carcinoma. In case 2, tissue breakdown products, formed in consequence of the heavy x-irradiation of the cancerous breast and adjacent lymphoid areas, may have caused the granulomatous reaction. In case 3, the lymph node granulomatosis may have resulted from liberation of some irritant through the destructive effects on the thyroid parenchyma of the chronic thyroiditis and of the carcinoma; mention has already been made of the occurrence of granulomatous foci in the regional lymph nodes in some cases of thyroiditis. In cases 4 and 5, bronchial obstruction was associated with retention of secretion, but there was nothing suggestive of any irritant effect of the latter; moreover, only in case 5 were there any granulomatous lesions in the lung, and they had not developed in close relationship to the retained secretion. As sections stained to demonstrate fat were not available, it could not be confirmed that the foamy cells in the lung in case 5 were lipophages; if they were such, the source of the ingested lipid is not apparent. It is noteworthy that in neither of these cases had there been any investigation or medication involving administration of oily substances which could have been inhaled.

Such an association of neoplasia with apparently non-infective, tuberculoid granulomas in the related lymphoid tissue probably is not particularly rare: the cases reported here were seen within a period of 6 months in a department dealing with approximately 350 major surgi-

cal specimens a month, of which about one-fourth are neoplasms. Nevertheless, apart from Gherardi's case,[1] I know of no description of this association; it may, however, have been present in one, at least, of a series of cases reported by Moak [9] as examples of coexistent carcinoma and tuberculosis. In 2 of Moak's cases of cancer of the breast, metastatic carcinoma and "tubercles" coexisted in the axillary lymph nodes; the "tubercles" consisted of epithelioid and giant cells, in one case without necrosis and in the other with "commencing degenerative changes" at the center of a small minority of the lesions. A few tubercle bacilli were found, with difficulty, in the first case; staining for tubercle bacilli could not be carried out in the second.

Asteroid Bodies. Asteroid bodies were present in the cytoplasm of some giant cells in all 5 cases. These stellate inclusions were described originally by Goldmann [10] in 1890, in relation to a dermoid cyst. They appear not to have attracted much further attention until they were described in 1911 by Wolbach,[11] in cases of the condition which has become known as Stengel-Wolbach sclerosis. The most recent accounts appear to be those by Friedman [12] and Kay,[13] both of whom studied these structures in cases of sarcoidosis of the spleen, with which the last-named author considered Stengel-Wolbach sclerosis to be identical. The nature of these inclusions is obscure; they occur in the cytoplasm of giant cells in a number of conditions, and they are not of diagnostic significance. It is of interest that, in the present series of cases, the "asteroids" were most numerous in that case (case 2) in which the region drained by the affected lymph nodes had been subjected to intensive x-irradiation over a period of 19 days immediately before the operation at which the specimens were obtained.

Schaumann Corpuscles. The irregularly scalloped or spheroidal inclusions called Schaumann corpuscles,[14] which are usually heavily calcified and often concentrically laminated, double contoured, and sometimes anisotropic, and which are found within the giant cells in some cases of sarcoidosis and occasionally in lesions of known mycobacterial causation, were not found in any of the cases reported here. The results of histochemical investigations now proceeding do not support the view expressed by Teilum [14] that asteroid bodies may be of the same nature as inclusions of the Schaumann type.

Paramyloid Deposits. In the granulomatous lymph nodes in case 2 there was a moderate amount of homogeneous material in and near the tuberculoid foci. The staining reactions of this material suggested that some of it was of the nature of paramyloid, as described by Teilum [15] in sarcoidosis and other conditions associated with hyperglobulinemia.

Teilum considered that the lesions of sarcoidosis represented the result of an allergic hyperglobulinosis of the reticulo-endothelial system, determined by persistent or repeated stimulation of immune mechanisms, with precipitation of paramyloid which becomes transformed into hyaline material. It is unfortunate that no investigation of the serum proteins was carried out in case 2. In none of the other cases here reported were deposits of paramyloid seen, although hyalinization was present. It is of interest that the paramyloid in case 2 showed affinity for Congo red, although it did not stain metachromatically with methyl violet, while the asteroid bodies in this case stained both with Congo red and metachromatically pink with methyl violet.

Hashimoto's Disease (*Struma Lymphomatosa*) *and Carcinoma of the Thyroid Gland.* The association of a primary thyroid carcinoma with Hashimoto's disease, seen in case 3, has not, to my knowledge, been reported previously, although Dinsmore and Hazard [16] described an undifferentiated carcinoma originating in a thyroid gland, of which, they suggested, the dense, peripheral sclerosis might represent Riedel's disease.

Summary

Neoplasia and granulomatous inflammation may coexist in one site or in one region of the body. This coexistence may be fortuitous, but occasionally neoplasia may develop as a complication of chronic granulomatous inflammation or, more often, a granulomatous reaction may result from the presence in the tissues of irritant products released in consequence of the pressure effects or necrosis associated with growth of the neoplasm or of the action of therapeutic agents upon it. Such granulomas are often tuberculoid in structure and, particularly when they occur in lymphoid tissues, may so resemble the lesions of sarcoidosis that the latter may be erroneously diagnosed in the absence of adequate confirmatory evidence.

Four cases are recorded in which tuberculoid lesions without necrosis were found in lymph nodes receiving the lymphatic drainage from organs the seat of primary carcinoma (breast, 2 cases; thyroid gland, 1 case; bronchus, 1 case). In a fifth case, tuberculoid granulomas were present in the intrapulmonary lymphoid follicles in the vicinity of an invasive bronchial "adenoma." The granulomatous lesions are considered to have been the result of absorption of irritant materials from the tissues drained by the affected lymphoid tissue, and not a manifestation of a granulomatogenic infection or of the presence of any generalized disorder of the lympho-reticular system such as sarcoidosis. Intracellular asteroid bodies were found in the granulomatous lesions

in all cases, and paramyloid material was present in the lymph nodes in one case.

One of the 5 cases described appears to be the first recorded example of a carcinoma arising in the thyroid gland in association with Hashimoto's disease (struma lymphomatosa).

I wish to thank my colleagues in the Surgical and Radiotherapeutic Departments of the United Birmingham Hospitals for allowing me access to the records of patients under their care.

ADDENDUM

Since the submission of this paper Nadel and Ackerman [17] have described 5 cases in which sarcoid-like lesions were found in lymph nodes draining an area containing a malignant neoplasm. It is noteworthy that asteroid bodies were not found in any of their cases; in one case inclusions resembling those to which Schaumann's name is given [14] were present. These authors [17] reiterated Freiman's [18] plea for a distinction to be made between the "sarcoid lesion" and "sarcoidosis," the former being a non-pathognomonic histologic pattern of granulomatous reaction to any of a wide variety of injurious agents (including the still undetermined pathogenic agent of sarcoidosis itself), and the latter a systemic disease entity. It is unfortunate that these three authors,[17,18] when stressing the need for observance of this distinction, should continue to use the word sarcoid as descriptive of lesions which appear to have no relationship to sarcoidosis other than that of the histologic similarity of the individual granulomatous foci. A great deal of the confusion in thought and practice which clouds understanding of sarcoidosis has its roots in such misapplication of the word sarcoid to other conditions, and I feel that this word should be used only in reference to the systemic disease sarcoidosis and its lesions.

Nadel and Ackerman [17] referred to unpublished observations by Holman [19] of sarcoid-like lesions in the lymph nodes in a case of a cylindromatous tumor involving the tongue, and also to a case mentioned by Nickerson [20] in which similar lesions were found in the retro-aortic lymph nodes in a case of gastric carcinoma. Anderson [21] described as Boeck's sarcoid granulomatous lesions found in the lung and in a hilar lymph node in a case of metastasizing bronchial adenoma.

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[*Illustrations follow*]

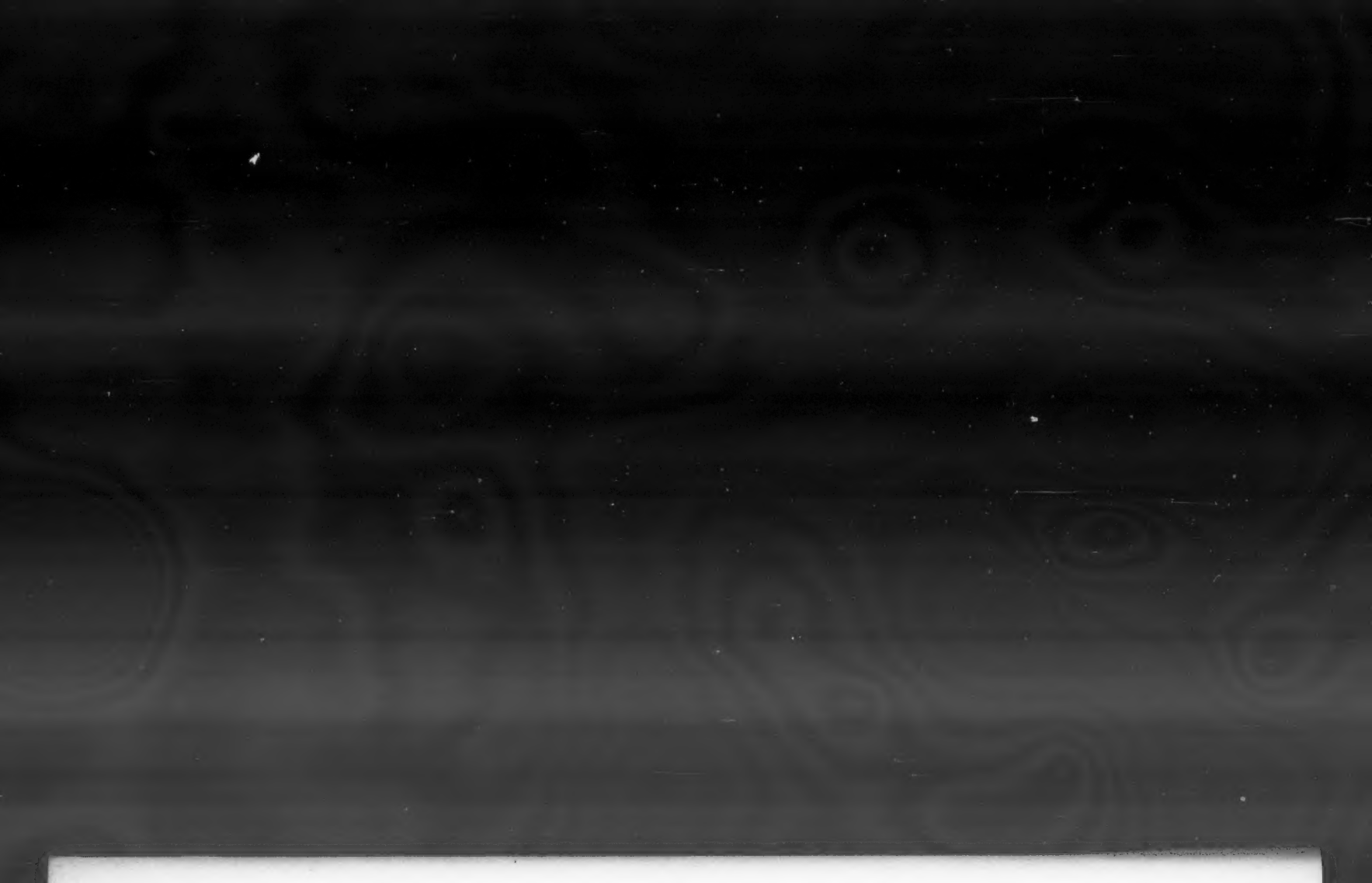
DESCRIPTION OF PLATES

PLATE 91

FIG. 1. Case 1. Section of the largest axillary lymph node. The tuberculoid foci appear as pale, sharply circumscribed areas in the upper part of the section. The ill defined, pale areas below and at the left side represent sinuses packed with proliferated littoral cells. Hematoxylin and van Gieson's stain. × 23.

FIG. 2. Case 1. Multinucleated giant cell containing many "asteroid bodies," each lying in a vacuolated cytoplasmic "pocket." Lawson's modification of Weigert's elastic tissue stain. × 800.

FIG. 3. Case 1. Tuberculoid focus in lymph node, with homogeneous hyaline material scattered through the adjacent lymphoid tissue. Hematoxylin and van Gieson's stain. × 200.



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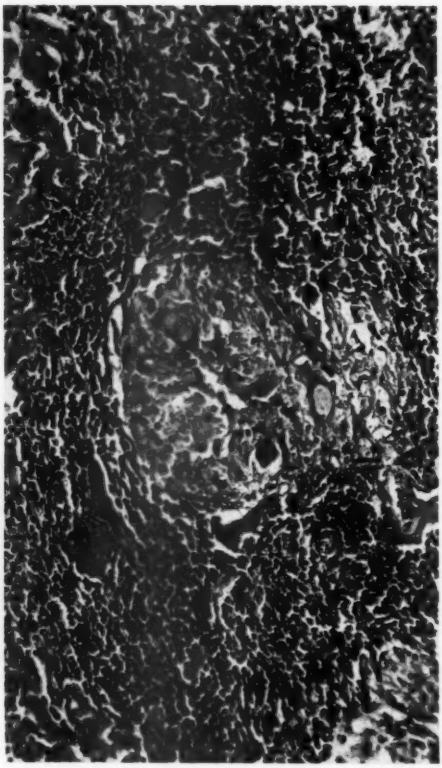

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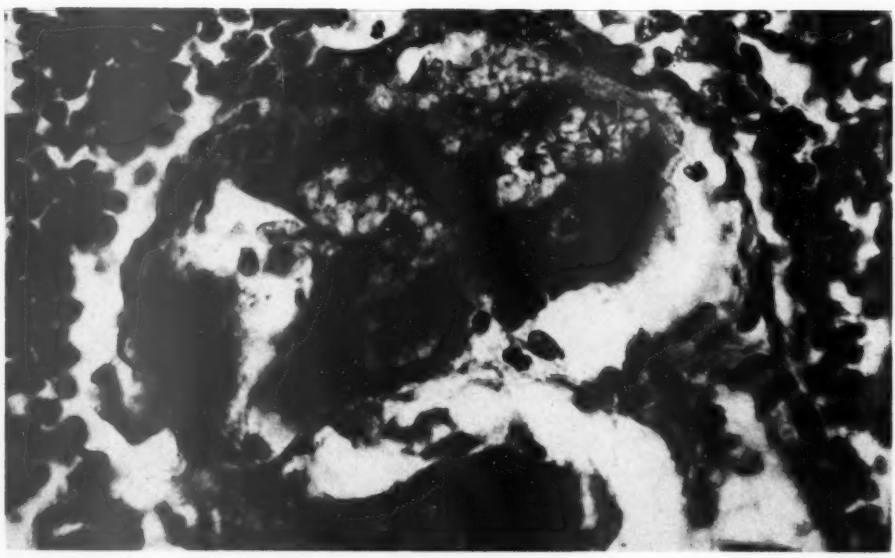

Symmers

Granulomas Associated with Carcinoma

PLATE 92

FIG. 4. Case 1. Epithelioid littoral-cell proliferation filling sinuses in a lymph node. Hematoxylin and eosin stain. × 200.

FIG. 5. Case 2. Tuberculoid granulomas and metastatic carcinoma in an axillary lymph node. Hematoxylin and eosin stain. × 100.

FIG. 6. Case 2. Giant cell containing a large "asteroid." Hematoxylin and eosin stain. × 800.

FIG. 7. Case 3. Anaplastic carcinoma of thyroid gland. Hematoxylin and eosin stain. × 64.

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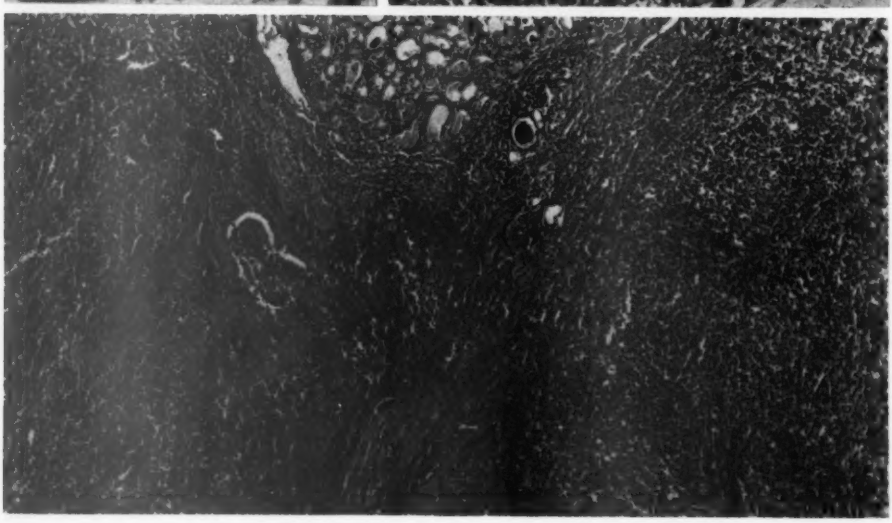

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PLATE 93

FIG. 8. Case 3. Clear cell trabecular area of thyroid carcinoma. Hematoxylin and eosin stain. × 172.

FIG. 9. Case 3. Multinucleated giant cells in a small tuberculoid focus in the peripheral part of an area of the thyroid gland recently involved by the carcinoma. Hematoxylin and eosin stain. × 200.

FIG. 10. Case 3. Area of left lobe of thyroid gland, showing diffuse lymphocytic infiltration and development of several lymphoid aggregates, in one of which a germinal center has formed. Hematoxylin and eosin stain. × 100.

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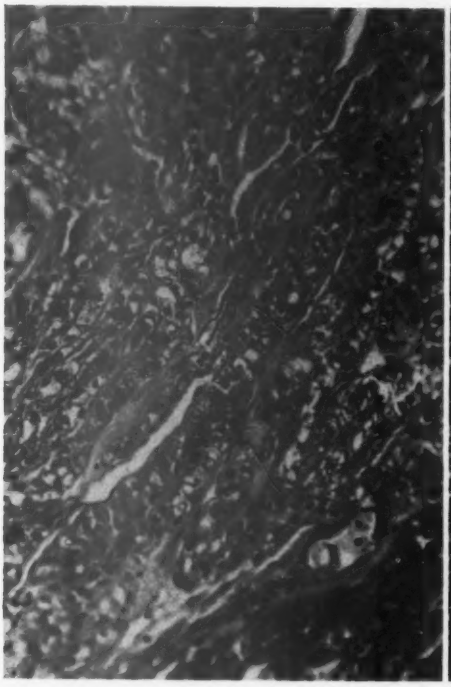

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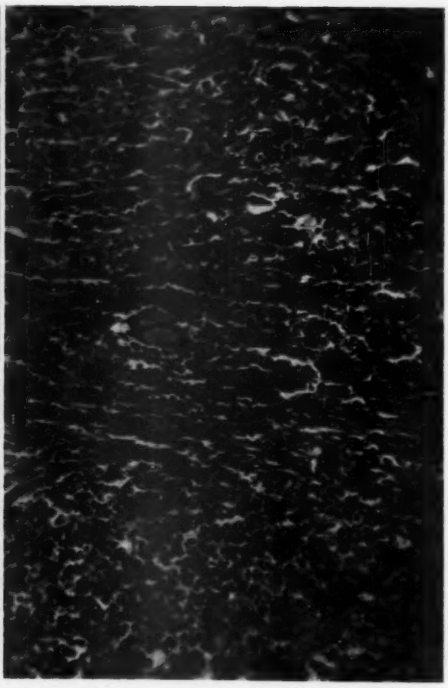

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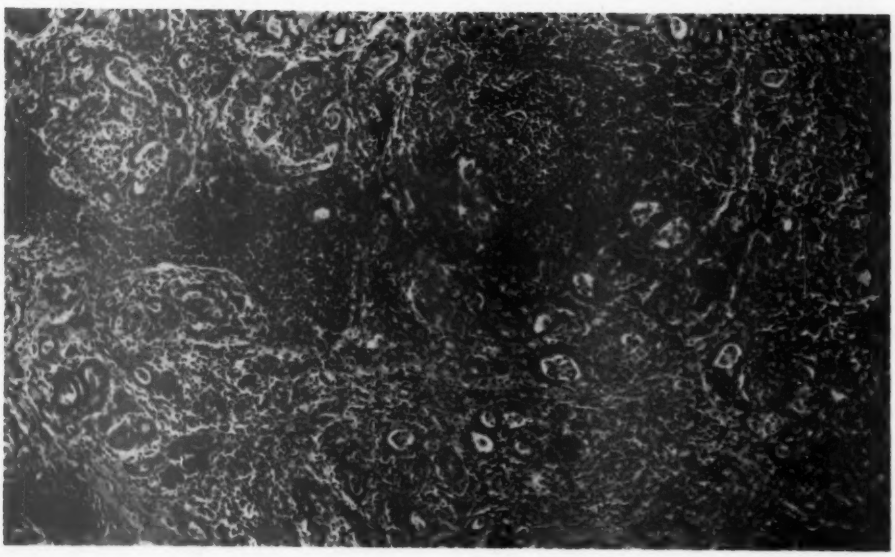

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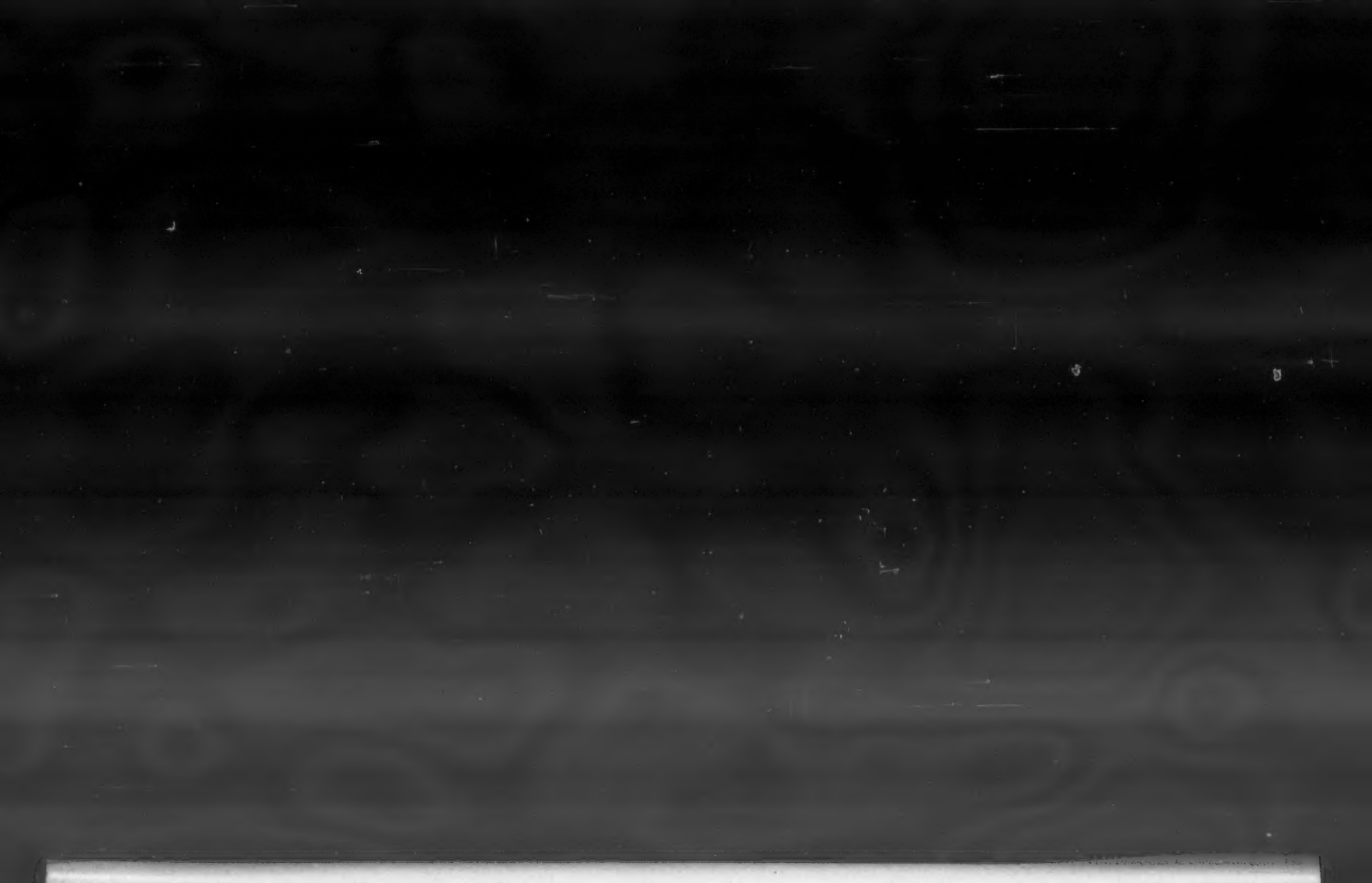
Symmers Granulomas Associated with Carcinoma

PLATE 94

FIG. 11. Case 4. Giant-celled histiocytosis of peripheral sinus of the lymph node. Hematoxylin and van Gieson's stain. × 200.

FIG. 12. Case 4. Tuberculoid focus in a sinus of the lymph node. Hematoxylin and van Gieson's stain. × 200.

FIG. 13. Case 5. Multiple tuberculoid foci in intrapulmonary lymphoid tissue. Hematoxylin and eosin stain. × 86.



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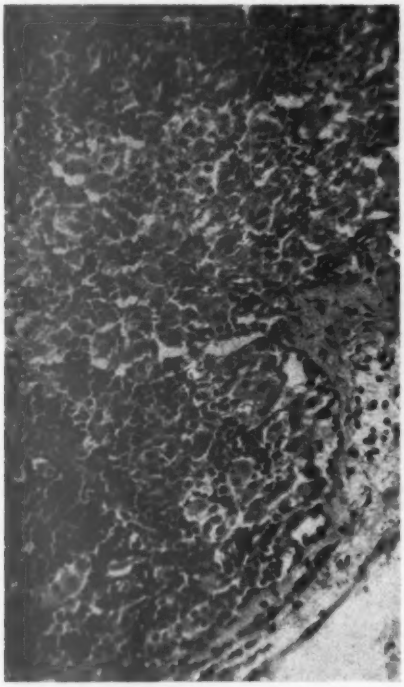

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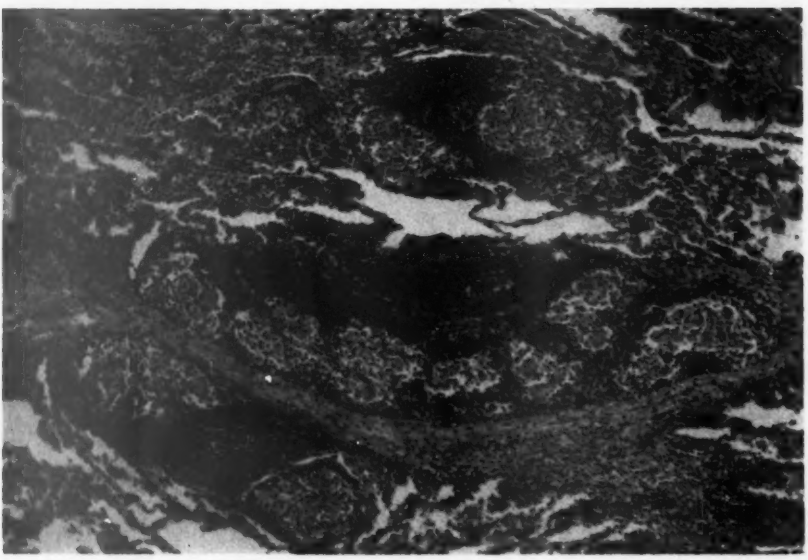

MALIGNANT MELANOMA IN THE TROPICS *

WILLIAM F. ENOS, CAPT., M.C., and ROBERT H. HOLMES, LT. COL., M.C.
(From the Board of Health Laboratory, Ancon, Canal Zone)

There is a current trend to accept the point of view that the nevus and hence malignant melanoma are of ectodermal origin. The disproportionate incidence of skin carcinoma of basal and squamous cell type in the white population as compared to the Negro is well established. It is, therefore, apropos to examine the racial incidence and comparative behavior of the most malignant of skin neoplasms, namely, malignant melanoma.

A review of the necropsy and surgical files at the Board of Health Laboratory, Ancon, Canal Zone, revealed 7 cases of malignant melanoma in which necropsies were performed, and 9 surgical cases diagnosed as malignant melanoma. Follow-up of these cases was successful in 6 instances. This review covered the period from 1904 to 1950, during which time 18,241 necropsies were performed and 54,362 surgical specimens received. It is immediately apparent that malignant melanoma, at least in this locality, is diagnosed very infrequently.

NECROPSY CASES OF MALIGNANT MELANOMA

Table I lists 7 cases of malignant melanoma, 5 of which occurred in Negroes and 2 in Caucasians; 3 were males and 4 females, varying in age from 29 to 99 years. It is of interest, even though this series is small, that 5 of these neoplasms occurred on the lower extremity; 4 actually on the foot. The lesion remained localized in one case and in 2 cases metastatic lesions were confined to the inguinal lymph nodes. These neoplasms occurred in persons 95, 52, and 99 years of age, respectively. The cause of death in each of these 3 cases was cardiovascular disease. The metastases to the inguinal lymph nodes were considered non-contributory to the cause of death. No relationship to trauma was elicited. The primary lesion varied from 1 cm. in diameter to a massive neoplasm extending over the entire medioplantar surface of the foot.

The primary lesion in cases 1, 2, and 7 occurred on the lateral and plantar surfaces of the foot. Cases 1 and 2 were similar in general appearance. In case 1, there was a large oval, black, sloughing lesion measuring 6.5 cm. in greatest diameter. In case 2 there was a large, elevated, mottled tumor measuring 12 cm. in diameter,

* Received for publication, July 28, 1950.

TABLE I

Necropsy Cases of Malignant Melanomas

Case no.	Age	Race	Sex	Location of primary lesion	Size of primary lesion	Metastasis	Duration	History of trauma	Cause of death
1	52	N	M	Lateral plantar, right foot	6.5 cm.	Right inguinal	24 mos.	None	Luetic heart disease
2	99	N	F	Lateral plantar, left foot	12.0 cm.	Left inguinal	Unknown	None	Cardiovascular
3	33	C	M	Face	1.5 cm.	General	Unknown	None	Malignant melanoma
4	76	N	M	Left thigh	10.0 cm.	General	20 mos.	None	Malignant melanoma
5	29	N	F	Medial surface, left great toe	Primary amputated	General	Unknown	None	Malignant melanoma
6	79	C	F	Vulva	Unknown	General	12 yrs.	None	Malignant melanoma
7	95	N	F	Plantar, left foot	2.0 cm.	None	Unknown	None	Cardiovascular

while in case 7 the lesion measured 2 cm. in diameter and was confined to the plantar surface of the foot.

The histologic pattern of the primary lesions in cases 1 and 7 exhibited what is believed to be a significant feature. Sections of case 1 obtained ante mortem showed a highly anaplastic melanoma with junctional change and epidermal ulceration. The subcutaneous tissue displayed solid sheets of invasive tumor cells arranged in nests and cords of hyperchromatic, pleomorphic melanoblasts. Atypical mitotic figures were plentiful and in many areas melanin was quite abundant, although totally lacking in others. A striking finding was the presence of many bizarre giant cells, many of which were multinucleated and possessed "comet-like" tailed processes of acidophilic cytoplasm. The giant cells varied from 20 to 40 μ in diameter and contained one to eight nuclei, occasionally coalesced or smudged, with one or two faintly acidophilic nucleoli. No pigment was noted within these cells, but cytoplasmic vacuoles were common. These features did not suggest fixation artifacts. Sections of case 7 were similar to those of case 1. Similar giant cells have been noted by Spitz [1] in her description of the juvenile melanoma. In sections of the inguinal lymph nodes,

melanin pigment and characteristic melanoblasts were present but no giant cells were noted.

Sections of the primary lesion were not available in case 2. The inguinal lymph nodes, however, contained nests and cords of moderately pleomorphic spindle-shaped melanoblasts. The density of pigmentation was variable. As in case 1, no giant cells were found in the metastatic lesion.

In case 3 the primary lesion was removed from the face prior to necropsy. In case 4 the primary tumor appeared as a mass in the left inguinal region measuring 8 by 6 by 4 cm. extending down the anterior medial aspect of the thigh. The tumor in case 5 was a fungating ulcerated mass involving the entire medial aspect of the left foot after amputation of the great toe.

The histologic pattern in cases 3 and 5 was similar to malignant melanoma as usually described. In case 4, however, giant cells again were encountered, although they were not so large or bizarre as those in case 1. Smudging of the nuclei and cytoplasmic vacuolation were absent. The metastatic lesions in this case also contained giant cells.

In case 6 the primary lesion had been described as arising from the vagina or cervix; however, sections taken from the vulva revealed an area of characteristic junctional change overlying invasive melanoma, and it seems more likely that the origin was at this site. Giant cells were observed also in this instance but, again, they were not so bizarre as in case 1, and did not show nuclear smudging, cytoplasmic vacuolation, or tailed processes.

Review of Surgical Cases

Of the 9 surgical cases of malignant melanoma studied (Table II), 5 patients were Caucasian and 4 were Negroes. Seven were males and 2 were females, varying in age from 26 to 70 years. Five of the lesions occurred on the lower extremity, 4 being on the foot and one on the thigh. Only one melanoma was found on the upper extremity, and that was located in the left deltoid region. Two tumors were located on the trunk and one on the face. The primary lesion varied in size from a small, flattened, pigmented area, 0.2 cm. in diameter, to a large, raised, fungating tumor, 7.5 by 3 by 6 cm. in diameter. History of trauma was elicited in 3 cases: a stone bruise, a burn, and a nail puncture. Five patients are living and well: 1 whose primary tumor was on the right cheek, 3 on the foot, and 1 on the trunk. Duration since excision varied from 1 to 3 years. Amputation of a foot with a large fungating, melanotic growth was performed in 1 case, and radical excision with skin graft was done in 2 cases. In the patient with amputation of the

foot, and also in one of the patients with radical local excision, inguinal metastases were found, but no evidence of visceral metastasis. Only one patient has succumbed with widespread involvement, and he was a 39-year-old Negro male with a small plantar lesion, historically related to a nail puncture wound. Data on subsequent course were lacking in 3 cases.

Cases 12, 15, and 16 were particularly interesting in that they occurred on the feet of elderly Negroes. These lesions, although appearing histologically as highly malignant melanomas, remained localized; or have metastasized, to date, only to the inguinal lymph nodes. No sections of the primary lesion were available in case 16; however, an inguinal lymph node revealed characteristic malignant melanoma. Two and one-half years following removal of this node in the Canal Zone, a fungating tumor was removed from the sole of the foot in the Bahamas and reported as a malignant melanoma. No visceral metastases were discovered at that time, 2½ years after diagnosis of the primary lesion, alleged to have followed a stone bruise.

A 54-year-old Negro (case 12) was admitted to the hospital with a large, ulcerated, melanotic tumor involving the medioplantar surface of the left foot and great toe. A specimen had been taken for biopsy from a flat, pigmented lesion of the margin of the left toe 2 years previously, and a diagnosis of malignant melanoma was made. At that time the patient refused amputation. During the recent admission, a low amputation of the foot was performed and a single, large lymph node was removed from the inguinal region. The tumor on the foot was an ulcerated, exophytic growth largely confined to the epidermis and upper corium with no evidence of extension into the deeper tissues. The lymph node was a deeply pigmented, black mass of relatively firm tissue showing complete replacement by malignant melanoma. Sections of the tumor presented an architecture dominated by bizarre giant cells similar to those described in cases 1 and 2.

In case 15, a recent "follow-up" revealed no local recurrence and no inguinal or visceral metastasis. The primary lesion in this case was excised radically, followed by skin graft approximately 1 year ago. The histologic pattern in this instance was that of a spindle cell neoplasm without giant cells. This lesion was said to be related to a recent burn at the site of origin.

In case 10, the lesion was also on the plantar surface of the foot and was said to follow a nail puncture. The patient was a 39-year-old male Negro who died 3 years after the original diagnosis, apparently with widespread metastasis. No necropsy was performed; however, inguinal

TABLE II

Surgical Cases of Malignant Melanomas

Case no.	Age at time of diagnosis	Race	Sex	Anatomical position of primary lesion	Size of primary lesion	Date of diagnosis	History of trauma	Data on subsequent course
8	44	C	M	Left hemi-thorax, 6th interspace	2.5 cm.	12–26–44	None	None
9	26	C	M	Right thigh	0.2 cm.	3–12–45	None	None
10	39	N	M	Plantar surface, right foot	1.5 cm.	5–31–45	Nail puncture	Died 2–13–48, general metastasis, no necropsy
11	29	C	M	Left deltoid region	Unknown	11–13–46	None	None*
12	54	N	F	Medioplantar surface, left foot	7.5 cm.	10–13–48	None	Foot amputated 9–17–50, metastasis to inguinal lymph nodes only
13	50	C	F	Left upper back	1.0 cm.	9–27–49	None	Living and well
14	49	C	M	Right cheek	0.6 cm.	1–6–49	None	Living and well
15	59	N	M	Posterior heel, right foot	1.2 cm.	3–28–49	Burn at site of lesion	Living and well; inguinal lymph nodes removed 4–15–50, negative
16	70	N	M	Plantar surface, left foot	2.4 cm.	6–14–47	Stone bruise	Inguinal lymph node removed 6–14–47; tumor excised 1–18–50; no evidence of visceral metastasis

* See addendum.

and abdominal masses as well as cerebral involvement were described clinically. The histologic pattern was that of anaplastic melanoma. No giant cells were noted.

Cases 8, 9, 11, 13, and 14 presented no unusual features in their histologic architecture as far as differential criteria for malignant melanoma are concerned.

Discussion

An excellent review of the natural history of the pigmented nevus has been afforded recently by Lund and Stobbe,[2] and certain unique features of juvenile melanomas have been emphasized by Spitz.[1] Anderson [3] and Allen,[4] independently, have suggested that the behavior of melanomas in the Negro race is somewhat unusual. Bishop,[5] Webster,[6] and Hewer [7] have reported on the frequency of melanomas in the Negro and the apparent predeliction of the foot as the site of origin. Wright,[8] in a series of 222 cases, stated that over one-half of the tumors of the lower limb were on the foot. Allen also has called attention to this fact in the South African Negro and indicated the possible significance of frequent trauma to bare feet. Evidence is accumulating which indicates that many factors are involved in the maturation of the simple mole and its more dramatic mutation to a malignant neoplasm.

In the present series, 7 necropsy cases and 9 surgical cases of malignant melanoma are reviewed and several facts appear significant. Exact ratios between the population groups of the Canal Zone are not available, but the estimated proportion between the white and black races considered as an average over the last 20-year-period is 1 to 2. The racial incidence in this series is 7 white to 9 Negro; therefore, if any conclusion can be drawn, the incidence is actually less among the Negroes than among the Caucasians.

There is a striking variation in the anatomical site of origin between the two races. All of the cases in the Negro occurred on the lower extremity, 8 on the foot and one on the mid-thigh. Among the cases in Caucasians, the foot was not involved in a single instance. Two lesions occurred on the face, two on the trunk, one on the genitalia, one in the deltoid region, and one on the thigh. This difference in topographic occurrence supports the observations of others and appears significant.

The relationship of trauma to the development of a malignant neoplasm usually is equivocal. In 3 of these cases, a history of trauma was available; namely, a nail puncture, a burn, and a stone bruise. In these particular instances, apparently no pre-existing nevus was present. Actually there was no history of a nevus in any of the Negro

patients, although 5 of the white patients described a mole with gradual enlargement and increased pigmentation. Of these, one was located at a site of irritation by a brassiere strap, a second was situated alongside a small scar resulting from a previously excised basal cell tumor of the skin, and one occurred in a patient who previously had had a basal cell carcinoma removed from a site other than that of the malignant melanoma.

Age of the patient appears to be a factor of some prognostic value. In the Negro past 50 years of age, as indicated by 7 of this group, the tumor has a strong tendency to remain localized or, at most, extend to the inguinal lymph nodes. Location of the lesion as well as degree of malignancy are apparently related to the age factor, as indicated by the finding that all cases involving the foot in the elderly Negro remained localized, whereas one Negro, 76 years old, with a primary lesion of the thigh, showed widespread metastasis, and in 2 young Negroes, 39 and 29 years of age, even though the primary lesion was on the foot, generalized metastases occurred.

An attempt has been made to establish approximate racial proportions. In this group of 16 cases, the distribution according to sex and race was as follows: 5 white males and 5 black males, 2 white females and 4 black females. No conclusion is indicated.

It is well known that the histologic pattern of malignant melanoma is highly variable. Just as the common mole exhibits a picture of orderly maturation with transition phases from one histologic type to another, so does the malignant melanoma display a varied character. There is the spindle cell type or so-called melanosarcoma, and the anaplastic epithelioid type or melanocarcinoma. Spitz [1] has focused interest on the prepubertal lesion or juvenile melanoma, which appears to have some subtle kinship with an endocrine factor. This lesion, it has been emphasized, usually remains localized, with rare metastasis. Although the juvenile melanoma presents a histologic appearance difficult to distinguish from the adult type of malignant melanoma, Spitz has described characteristic multinucleated and mononuclear giant cells with acidophilic cytoplasm, sometimes granular or vacuolated, not containing pigment. Multiple acidophilic nucleoli are common. Similar giant cells were found in 3 patients of this group. All were Negroes (cases 1, 7, and 12). The lesions were located on the plantar surface of the foot, and the ages were 52, 95, and 54 years, respectively. In case 1, the patient died of luetic heart disease with only inguinal metastasis; in case 7, the patient died of hypertensive cardiovascular disease with no evidence of metastasis; and in case 12 the patient is living and well with evidence of inguinal metastasis. This apparent tendency to re-

main localized or to have metastasis limited to inguinal lymph nodes, coupled with a histologic pattern strongly reminiscent of juvenile melanoma, is of considerable interest. Could it be that in some elderly persons, also, a subtle endocrinologic factor similar to that which appears to influence the juvenile melanoma, is effective in determining the behavior of the senile melanoma?

Summary

Among the 16 cases of malignant melanoma reviewed for this study, 9 occurred in Negroes. All of the neoplasms in Negroes arose on the lower extremities, 8 of them on the foot. When the primary was on the foot of an elderly Negro, the neoplasm remained localized or did not metastasize beyond the inguinal nodes.

The histologic pattern of certain senile melanomas is similar to that of the juvenile type, and an apparent similarity in behavior has been noted.

The prognosis in malignant melanoma is not always so hopeless as many believe. Clinical evaluation depends on careful consideration of the factors of age, location, and race.

Appreciation is expressed to Mr. Harry Dunn, photographer, Board of Health Laboratory, for his preparation of the photomicrographs.

ADDENDUM

Recently, the patient known as case 11 was admitted to the hospital because of a mass in the right lung discovered on "follow-up" roentgenograms. Thoracotomy was performed, tissue secured, and a diagnosis of malignant melanoma made.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 95

FIG. 1. Case 1. Multinucleated giant cells are similar to those occurring in the juvenile melanoma. × 900.

FIG. 2. Case 1. Multinucleated giant cells, showing irregular chromatin distribution, prominent nucleoli, and a granular acidophilic cytoplasm. × 900.

FIG. 3. Case 7. Patient 95 years of age. Multinucleated giant cell with "comet-like" tailed process of cytoplasm. × 900.

FIG. 4. Case 7. Multinucleated giant cells similar to that shown in Figure 2. × 900.

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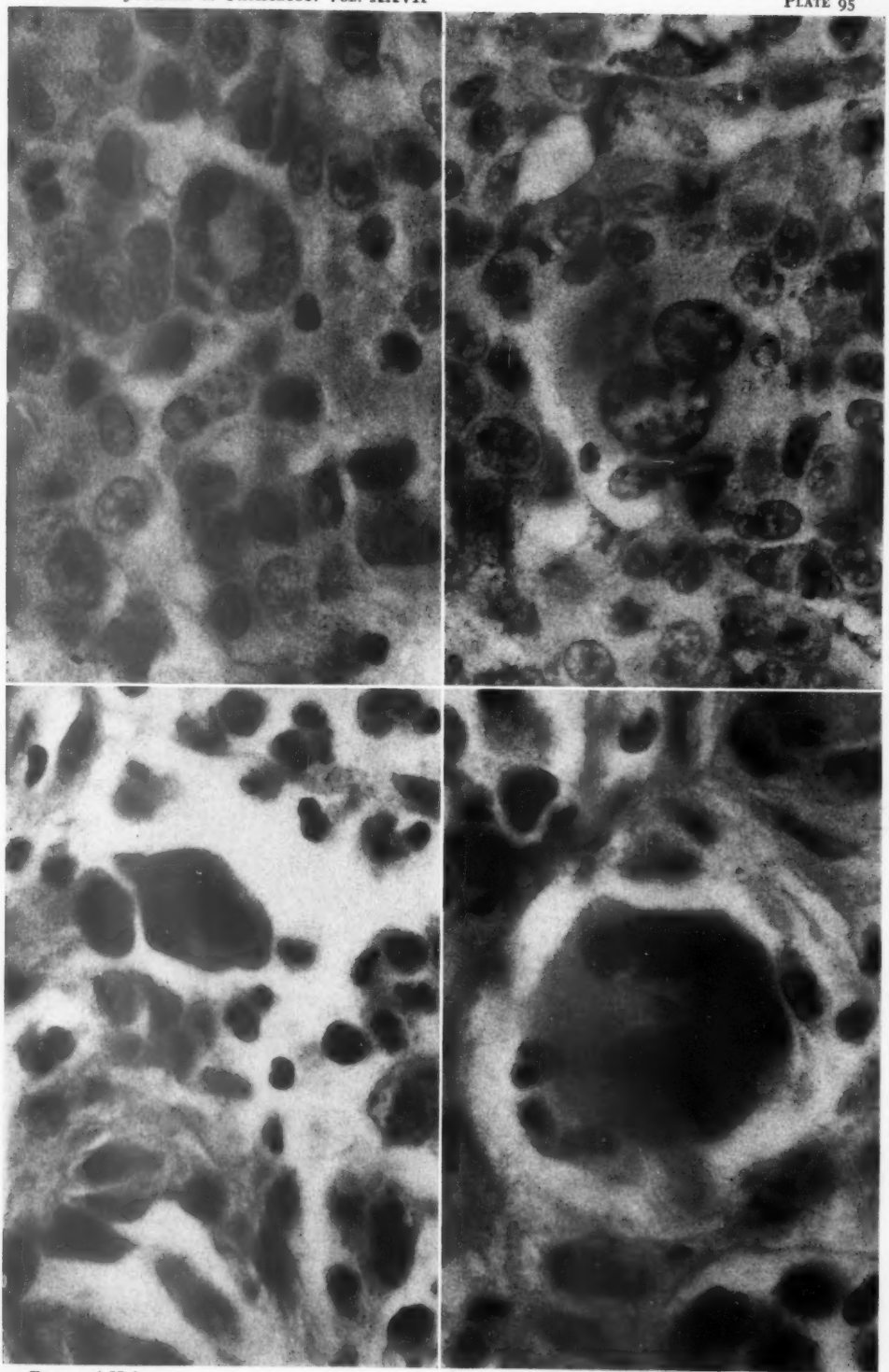
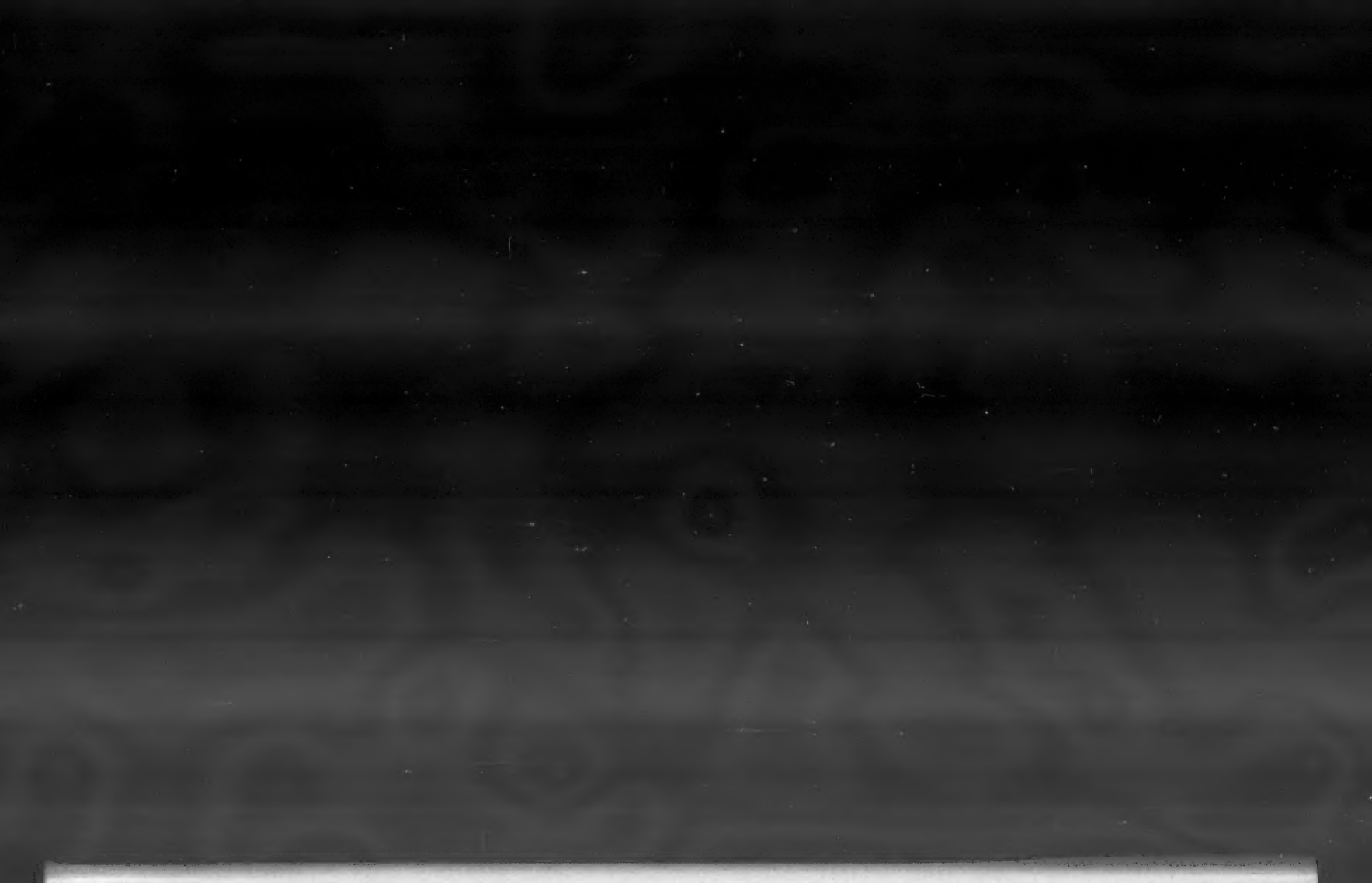


PLATE 96

FIG. 5. Case 12. Gross specimen and inguinal lymph node. No other evidence of metastasis.

FIG. 6. Case 12. Original biopsy specimen, showing marked junctional changes and loss of cohesiveness. × 200.

FIG. 7. Case 12. Multinucleated giant cells with vesicular nuclei.



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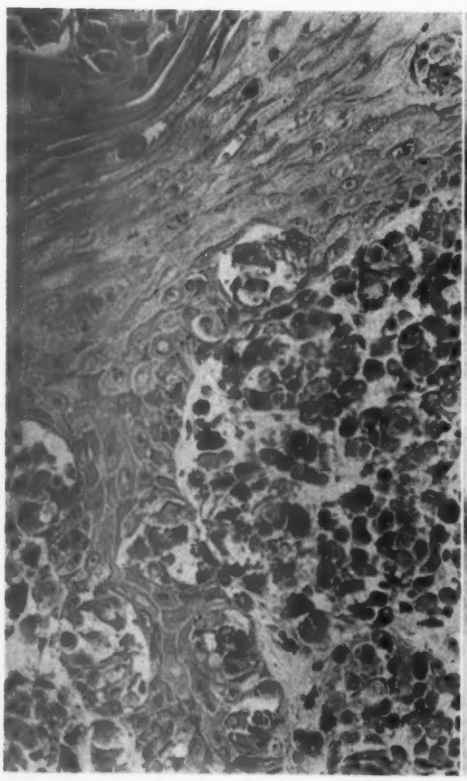

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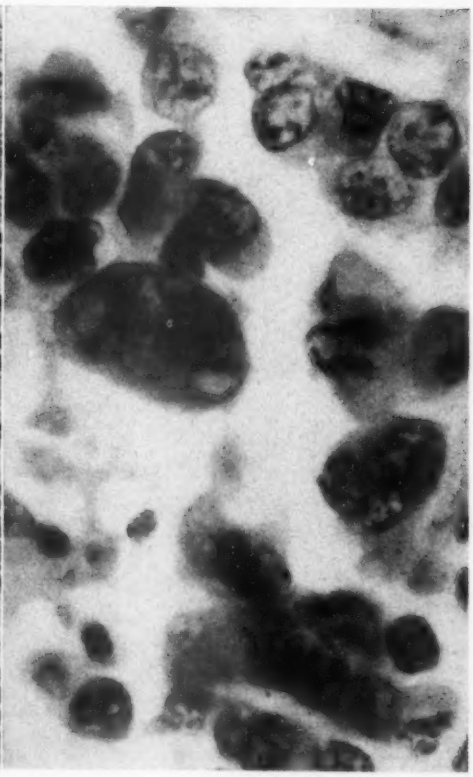

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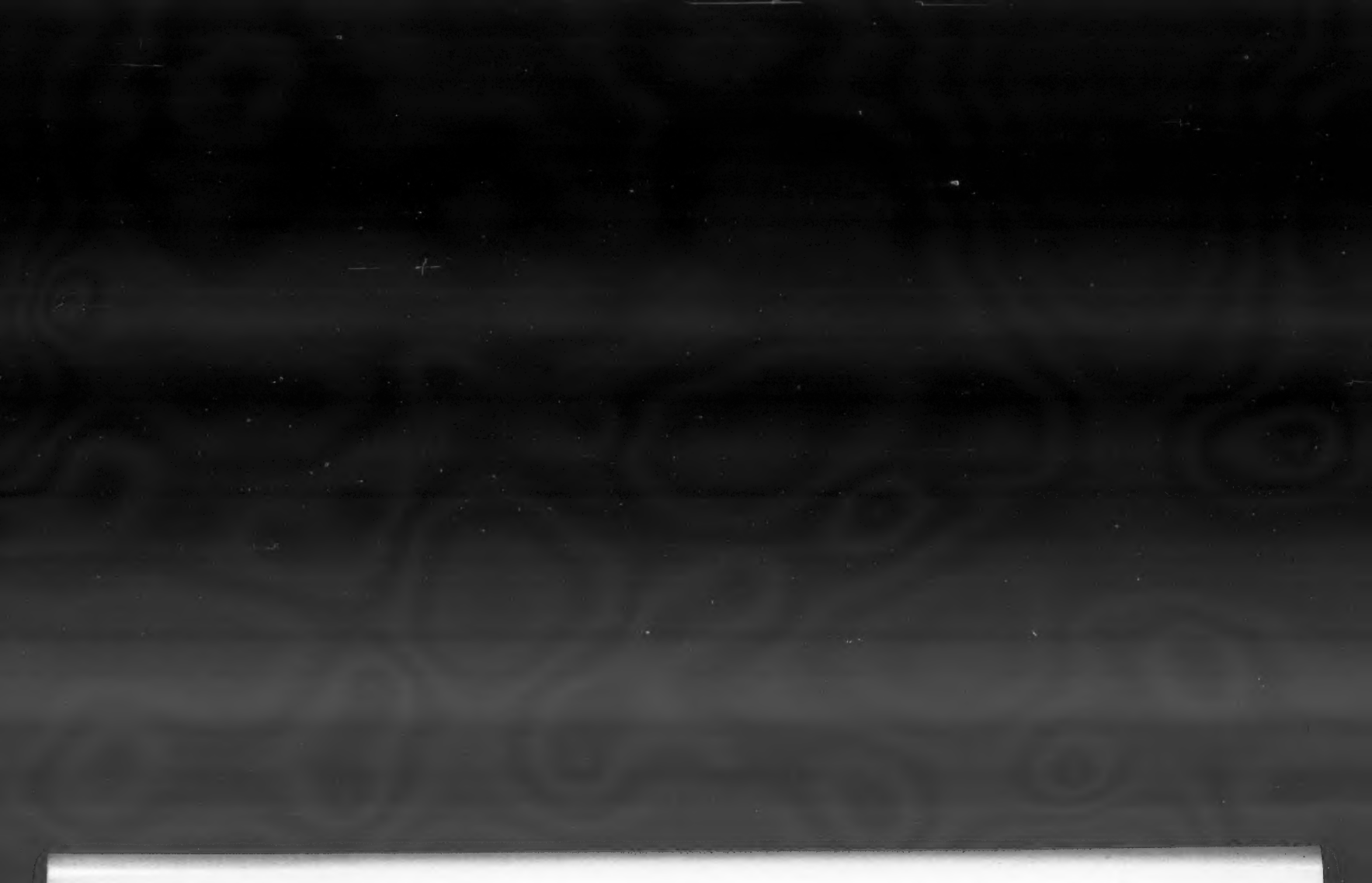
Malignant Melanoma in the Tropics